# FORMALDEHYDE: REVIEW OF SCIENTIFIC BASIS OF EPA'S CARCINOGENIC RISK ASSESSMENT

# HEARING

BEFORE THE

SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT

OF THE

COMMITTEE ON
SCIENCE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES

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# FORMALDEHYDE: REVIEW OF SCIENTIFIC BASIS OF EPA'S CARCINOGENIC RISK ASSESSMENT

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THURSDAY, MAY 20, 1982

House of Representatives,
Committee on Science and Technology,
Subcommittee on Investigations and Oversight,
*Washington, D.C.*

The subcommittee met, pursuant to recess, at 9:40 a.m., in room 2318, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee) presiding.

Mr. Gore. The subcommittee will come to order.

I would like to welcome all of our guests. I have a somewhat longer opening statement than usual, and I ask the indulgence of my colleagues and guests.

An anniversary is frequently a time for joy and reflection. Today marks the first anniversary of Ms. Gorsuch, the EPA Administrator, assuming the rein of control at the Environmental Protection Agency.

Upon assuming command at EPA, the Administrator criticized the quality of science at EPA and promised to improve it. But what have we seen at EPA during the past year? First, the administration recommended massive budget cuts for EPA, including, in real dollars, a 49-percent reduction in the Office of Research and Development budget over a 2-year period.

Next, we have witnessed staff reductions and departure from EPA of some of its most qualified scientists, demoralization of staff, and particularly scientific staff; who believe their advice is consistently ignored; and a belief, becoming widespread, that industry has special access to EPA and that EPA is becoming a captive to the industries it was established to regulate. These actions hardly seem calculated to improve the science in EPA's decisions.

Today then is certainly a time to reflect upon EPA's performance over the past year and assess whether it has enhanced the scientific basis of its decisions and upheld the integrity of the scientific process.

Among the most important statutory responsibilities assigned by Congress to EPA is that of protecting the public health from exposure to toxic substances. More than 55,000 chemicals, most of which have unknown effects, are in commercial production in the United States today.

Under the Toxic Substances Act, EPA must determine which chemicals should be regulated because they may present an unreasonable risk to public health and the environment. This is, of course, not an easy task. Any decision involves three basic steps: One, determining the nature of the health risk posed by the chemical; two, determining the extent of that risk to the public; and, three, determining what control measures, if any, are appropriate.

The first two steps are primarily scientific, and they are the focus of today's hearing. Today, in a narrow sense, we will be reviewing EPA's recent scientific determination not to regulate formaldehyde under section 4(f) of TSCA.

Formaldehyde is ubiquitous; it is used in mobile homes, plywood and particle board, permanent press fabrics, embalming fluids, and furniture, among other products. Approximately 7 billion pounds of formaldehyde are produced each year, making it the 26th largest volume chemical produced in the United States. Virtually the entire U.S. population is exposed to formaldehyde, millions at what may be significant levels. In this context, EPA's decision takes on enormous importance.

But however important the formaldehyde decision is itself, its significance is dwarfed by its implications for future Federal decisions on potential carcinogens. EPA's decision discounts more than a decade of science and experience by Federal agencies during which careful peer and public review led to widespread acceptance of principles for assessing the human risk from potential chemical carcinogens.

According to a recent report of the Office of Technology Assessment, all Federal agencies accept a "positive bioassay result in a single species as evidence that the substance is a potential human carcinogen." Likewise, all Federal agencies "do not accept the idea of thresholds in making decisions about carcinogenic risks" and believe that they "should not wait for epidemiological evidence before taking action to limit human exposure to chemicals considered to be carcinogenic." These principles are widely accepted in the non-Federal community as well. They have long been established.

In its formaldehyde decision, EPA apparently has rejected these widely accepted principles and done so without any public debate, without any open peer review.

The issue we examine today is really quite simple: Can an agency, without scientific support, without public review, change the basic scientific presumptions on which all Federal environmental health laws have been based, presumption that requires, in the absence of scientific certainty, that we follow a precautionary approach and protect the public from exposure to carcinogenic substances?

The simplicity of the question, though, belies its significance. On February 10, 1982, Dr. John Todhunter, EPA's Assistant Administrator for Pesticides and Toxic Substances, sent a memorandum to the EPA Administrator recommending that no action be taken on formaldehyde under section 4(f) of TSCA.

This recommendation was at variance with that made by the EPA staff in May 1981, the time Ms. Gorsuch took over at EPA. Because the chronology is important to understanding the scientific issues before the subcommittee, I would like to briefly review the events.

First of all, in the fall of 1979 the Chemical Industry Institute of Toxicology [CIIT] notified EPA of some preliminary findings in its animal bioassay on formaldehyde. The National Toxicology Program convened a panel of distinguished Federal scientists to review the CIIT study and other evidence on formaldehyde.

In November 1980—a year later—this Federal panel concluded that formaldehyde was an animal carcinogen and should be presumed to be a human carcinogen.

Upon receipt of this information, EPA determined that section 4(f) of TSCA was triggered, requiring EPA, within 180 days, to initiate action on formaldehyde or to publish a public notice of the reasons it would not take action.

The EPA staff reviewed the evidence on formaldehyde and wrote up their findings in a priority review level one document [PRL-1] dated February 19, 1981. The staff recommended that EPA designate section 4(f) as applicable to formaldehyde. The recommendation was based on the PRL-1 and was on the Administrator's desk within the 180-day statutorily mandated deadline, May 1981, approximately the time that Ms. Gorsuch arrived.

In May the Administrator asked Dr. Hernandez, EPA's Deputy Administrator, to evaluate the evidence on formaldehyde. In conjunction with the Formaldehyde Institute, an association of formaldehyde producers, Dr. Hernandez convened three science courts, one each in June, July, and August 1981, to review the evidence on formaldehyde. These meetings were not publicly announced. Other than industry associated lawyers and scientists and EPA scientists, only three other people attended any of the meetings, two from the National Academy of Science and one from Oak Ridge Labs.

In September 1981 Donald Clay, director of the Office of Toxic Substances, which is under Dr. Todhunter, sent a memorandum to Dr. Todhunter recommending against taking action on formaldehyde under section 4(f). An options paper which analyzed the scientific and policy questions and set out the staff opinions on various scientific issues was attached to the Clay memorandum. The options paper was based primarily on the PRL-1, the Hernandez meetings, and other staff analysis.

Under Dr. Todhunter's supervision and with his direct involvement, the PRL-1 was revised and appeared as the technical document in November 1981. The Todhunter memorandum of February 10, 1982, was apparently not reviewed by the staff at OTS.

Dr. Todhunter's memorandum presumably rests on the November version of the technical document and the Clay memorandum, although in fact much is contained in the Todhunter memorandum which was rejected by the staff for inclusion in the technical document.

Central questions for the subcommittee's examination will be:

To what extent has Dr. Todhunter relied upon EPA's scientific staff and its Science Advisory Board in reaching the conclusions on the scientific evidence concerning formaldehyde?

To what extent has EPA and Dr. Todhunter departed from the long-standing principles for carcinogenic risk assessment and given the wide acceptance of these principles is there an accepted scientific basis for such departure?

To the extent that neither the technical document nor the Clay memorandum agrees with Dr. Todhunter's decision document, what were Dr. Todhunter's sources of information?

And to what extent did the EPA's decision receive peer review or public input?

To the extent that EPA has departed from established scientific principles, the burden of proof rests on EPA to establish the scientific validity of its departure and to arrive at such a conclusion in a manner that preserves the integrity of the scientific process and the Federal decisionmaking process.

I anticipate a long, difficult, and complicated hearing, and I would like to now turn to my colleague, the ranking minority member, Mr. Walker, who, I would not be surprised to see, views these events in a different context.

Mr. Walker?

Mr. **Walker**. Thank you, Mr. Chairman. I intend to complicate things a little here from the start.

Mr. Chairman, I must protest the hearing here today. Regardless of the way in which the purpose of the hearing is phrased, it is impossible to escape the conclusion that this hearing is an attempt to go completely beyond our committee jurisdiction and to interject this committee into the regulatory process at the Environmental Protection Agency.

There is a story about Abraham Lincoln that seems to apply here today. Once when he was President, Lincoln asked his Cabinet how many legs did a cow have. They responded, of course, that a cow had four legs. "Well," said President Lincoln, "if we call a tail a leg, then how many legs does the cow have?" The Cabinet immediately said that in that case the cow would have five legs. "No," said Lincoln, "it does not matter what you call the tail; a cow still only has four legs."

Just like Mr. Lincoln's cow, Mr. Chairman, we cannot capture jurisdiction where none exists just by calling a tail a leg.

What particularly concerns me about this hearing is that it seems to be an obvious result of the efforts of a few disloyal and disgruntled employees of the EPA who have decided that, since they were disappointed when the proper officials within EPA decided not to nominate formaldehyde under section 4(f) of the Toxic Substances Control Act for priority regulation, they feel justified in waging guerrilla warfare against the Agency and those in positions of authority.

Rather than take a stand on principle and resigning and fighting a decision with which they disagree, openly and honorably, they seem to have stayed within the Agency pretending to be loyal employees while they wear a path to the Xerox room in their haste to photocopy everything and anything that they think then might be used against those who have the audacity to disagree with them.

These faceless, nameless cowards then indiscriminately leak this information to anyone they think might be manipulated to their advantage. I feel that this subcommittee is being so used by outside influences.

Mr. Chairman, I do not know what the other members of this committee might do or think in similar circumstances, but if I found one of my employees engaged in a program of photocopying my files, including my private notes and personal calendar, and using those photocopies against my interests, I know what I would do. People who have no loyalty and have no honor are beneath contempt. People who lack the courage of their convictions and who are unwilling to stand up in the light of day and fight for what they think is important also lack credibility.

We are not dealing with some new and unknown chemical here; we are dealing with one of the most common chemical substances known to man. We are dealing with a chemical substance which occurs naturally in nearly every human being—or in every human being. We are dealing with a chemical which is produced by tons by automobiles and airplanes. This is a chemical which you create each time you turn on your gas stove.

The economic consequences of a ban on formaldehyde are enormous. I have here a list of more than 100 products which contain formaldehyde, which range from plywood to permanent press fabrics and include such things as shampoos, cosmetics, nylons, from diaper liners to embalming fluids.

Mr. Chairman, I would ask that this list, which is not an all-inclusive list of the products which contain formaldehyde, be included in the record at this point.

Mr. GORE. Without objection, it is so ordered.

[Material to be supplied follows:]

## PRODUCTS CONTAINING FORMALDEHYDE

- Particle board
- UF Foam insulation
- wax and butcher wet strength paper
- perma press cotton
- plastic
- plywood
- molding compounds
- fiberglass and mineral wool insulation binders
- formica
- pressed wood furniture
- brake drums
- plastic parts for vehicles
- plumbing fixtures
- hardware
- lawn and garden equipment
- sporting goods
- counter and table tops
- melamine tableware
- resins and oil based paints
- explosives
- vinyl resins
- electrical insulation parts
- nitrogen fertilizers
- phenolic termasetting resins
- tire rubbers
- insecticides
- pharmaceuticals
- textile treating agents
- detergents
- water softening chemicals
- urethane coatings and resins
- antihistimines
- aerosol insecticide
- dyes for textile industry
- embalming agents
- anti-perspirant formations
- oral hexamethlenetetramine medication
- drinking milk
- dental filling
- dust sterilizing solutions
- hair waving preparations
- deodorants
- nail hardener
- glues
- acrylic
- wool
- nylon fibers
- photo chemical smog
- cigarette smoke
- mascara and other cosmetics
- barber and beauty shop disinfectants
- air fresheners
- dry cleaners for disinfectant
- fiber board
- air and furnace filters
- furniture adhesives
- binding on paper bag seams
- plaster of paris castings
- orthopedic casts and bandages
- binders for sand foundry cores
- coated papers used for cartons and labels
- coatings for appliances
- primer coats for automobiles
- paint and wood,finishes
- housings for electric shavers and mixers
- electronic equipment
- soap dispensers
- stove and refrigerator hardware
- toilet seats
- knob and buttons
- utensil handles
- shampoo
- nail polish
- mildew prevention
- synthetic lubricants
- textile water-proofing
- flour preservative
- wheat grains and agricultural seeds
- facial tissues and napkins
- hospital bed sheets
- examining table paper rolls
- dental bibs
- diaper liners
- some filter papers
- rayon
- drapery and upholstery fabrics
- carpet and upholstery latex backing
- non-woven binders and flock adhesives
- softeners and lubricants
- flame retardants
- anti-slip agents
- antistatic agents
- bactericides and napping agents
- sanforized cottons
- leather tanning
- preservatives
- vaccines
- automotive exhaust
- water filters

Mr. **Walker**. What astonishes me about this entire process is that we are hearing from a group of advocates who are essentially in favor of a no-risk regulatory philosophy. In essence, they are advocating a position which says that, since we cannot accurately quantify the risks involved, then we must regulate formaldehyde to protect those possible unknown victims.

While this argument has a certain potential for most politicians, I must ask if the risk is real—and I do not rule that possibility out—then where is the data to support that claim? The exposure charts in all of the published studies agree that there are four groups with particularly high exposure rates: biology students, workers in formaldehyde production facilities, morticians, and pathologists.

For a chemical which has been widespread in use for nearly 100 years, I would presume that if there is a real problem it should have become obvious by now. I can accept that among some students or unskilled workers a higher than average rate of nasal cancers might not be readily apparent, but morticians are an easily identified group in our society, and if they were regularly developing nasal cancers, I would think that that would be obvious, and, more importantly, pathologists are a group of highly trained medical doctors who specialize in discovering cancers. They meet on a regular basis. They are scientists who are in the habit of meticulously recording all of their findings and publishing the results of their studies.

But my research of the literature for positive clues in this matter only turns up negative findings. Despite all of the intellectual probabilities that formaldehyde may be a carcinogen in man, the evidence shows no pattern that really exists that it is a carcinogen, and I find any such thing very difficult to find any literature on.

In fact, an American Cancer Society report in February of this year stated that there is no such proof. I would ask unanimous consent for this material to be included in the record at this point.

Mr. **Gore**. Without objection, it is so ordered.

[Material to be supplied follows:]

08

AMERICAN CANCER SOCIETY, INC.
777 THIRD AVENUE • NEW YORK, N.Y. 10017 • (212) 371-2900

RESEARCH
EDUCATION
SERVICE

## American Cancer Society Statement Regarding

## Formaldehyde

The American Cancer Society has received numerous inquiries about whether or not formaldehyde (HCHO) can cause cancer in humans. Because of this, the Society asked a panel of distinguished scientists to review available scientific data; one published study showing that HCHO can cause cancer of the nasal turbinates in rats: a letter from Dr. Arthur Upton to a group of government agency officials alerting them to observations of the animal carcinogenicity of HCHO in his laboratory; and analysis of a Chemical Industry Institute of Toxicology (CIIT) report, by the Environmental Cancer Information Unit of Mt. Sinai Hospital, New York City.

Because of this animal data -- there is no evidence of carcinogenicity in humans -- and in response to the numerous inquiries, the Society believes it should make this information known to the public, particularly those who produce, work with, or use this important substance, and who are exposed to HCHO over lengthy and repeated periods of time.

HCHO is one of the most important and abundantly produced chemicals (several billion pounds a year in the USA alone) in American industry. Its users include the manufacture of adhesives for granulated wood and plywood, ureafoam for household insulation, and substances for permanent press fabrics. Small amounts of HCHO are produced naturally within the body and are quickly converted to formic acid and excreted in the urine. People also may be non-occupationally exposed to indoor air contamination by breakdown substances of HCHO products.

Available laboratory data shows a dose relationship in which more animals which are exposed to the highest level of HCHO developed cancers than did those exposed to lower amounts. It is important to note that unlike most other chemical studies in animals, HCHO produces cancer in rats and mice at doses which are reasonably comparable (only 2 to 3 times higher) to those to which people may be exposed in high exposure situations.

The Society will continue to support research on the potential carcinogenicity of HCHO in people and urges other research agencies to support such studi as well. The American Cancer Society, in the public interest, will continue to monitor the scientific evidence as it becomes available. We urge regulator agencies to do the same and to set appropriate standards to minimize occupatic and public exposure to the chemical, its industrial products and applications, based on scientific evidence.

February, 1982

Mr. **Walker**. I suspect that what is happening is that the average person cannot and will not tolerate more than four or five parts per million in the air we breathe. When the levels of formaldehyde reach that point, people have adverse effects, such as drying of mucous membranes, headaches, coughing, and feeling compelled to leave an area where the formaldehyde is confined.

On the other hand, the CIIT studies, which we will hear more about throughout this day, all point to the fact that formaldehyde will cause cancer in rats if they are exposed to high levels of the chemical, 15 parts per million, for prolonged periods of time.

As someone said to me last week, if you practically burn their noses off, they will eventually get cancer.

The lack of positive data on human carcinogenocy leads me to think that there are some entry level plateau to which most humans never reach, and that may also indicate that the actual risk to the general population may be almost nonexistent. And that is really what this hearing should be all about.

Under the Toxic Substances Control Act, the Administrator of the Environmental Protection Agency is required to make a determination if a particular chemical— formaldehyde in this case— poses a significant threat to the population, it requires immediate regulation.

I submit to each of you that, based upon a review of the evidence, it is possible to conclude that the possibility of risk posed to the population by formaldehyde is not significant. I do not claim that there is no risk. At least this far, it seems to be obvious to me that the data are not complete, but based on the data that are available, a reasonable man cannot conclude that the risk is not significant.

Based upon that, I reiterate my earlier charge that we are entirely out of our proper jurisdiction. We have no jurisdiction to question decisions which are regulatory in nature, and a decision not to regulate is just as much a regulatory decision as a decision to regulate. It is obvious to me that the purpose of this hearing is mostly a fishing expedition, with hopes of turning up something which the opponents to the current administration hope might help them reverse a decision already made.

I want the record to accurately reflect the fact that I think that this is unacceptable. It is totally beyond the rules of the Committee on Science and Technology and beyond the rules of the House.

Thank you very much, Mr. Chairman.

Mr. **Gore**. Thank you very much.

The record will reflect the gentleman's protest and the gentleman's view of the jurisdictional issue. I continue to appreciate the chance to work with my colleague, and I want to assure him that we have very carefully looked at the jurisdictional issue, and we have spoken with the counsel of the full committee and with the chairman of the full committee and received their opinion that they do not believe there is any controversy about it, but I respect the gentleman's opinion.

Mr. **Walker**. Thank you, Mr. Chairman.

Mr. **Gore**. I would like to call our first panel.

Dr. Norton Nelson, professor of the Institute of Medicine at NYU; Dr. Sidney Weinhouse of Temple University School of Medicine, the Fels Research Institute; Dr. Richard Griesemer, director of the Biology Division at Oak Ridge National Laboratory; and Dr. Kenny S. Crump, president of Science Research Systems, Inc., at Ruston, La.

If you would come up and take your places at the witness table, let me correct myself and say that Dr. Weinhouse held, among other positions, the chairmanship of the Subcommittee on Carcinogenesis Risk Assessment of EPA's Scientific Advisory Board, but he is unable to attend this hearing because of illness. A copy of his letter to EPA and his testimony, without objection, will be put into the record at this point.

[Material to be supplied follows:]

TEMPLE UNIVERSITY
OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION
SCHOOL OF MEDICINE
3420 NORTH BROAD STREET
PHILADELPHIA, PENNSYLVANIA 19140

FELS RESEARCH INSTITUTE
(215) 221-4300

December 28, 1981

Dr. John W. Hernandez
Deputy Administrator
The Environmental Protection Agency
401 'M' Street, S.W.
Washington, D.C. 20460

Dear John:

I was sorry to learn recently from documents I received from Arthur Upton, that the EPA (and possibly other regulatory agencies) are planning not to take action on formaldehyde, despite the evidence provided by recent assays in rats and mice. I believe this would be a grievous mistake John, for two reasons. It would not be compatible with accepted, well-founded and established principles; and would thereby run the risk of placing the EPA in an unenviable position of conflict with virtually everyone in the scientific community that is knowledgeable in the conduct and interpretation of experimental carcinogenesis assays. It would also create a precedent that would tie the hands of the agency in its possible future actions on other potential human carcinogens.

I understand and in fact applaud your reluctance to make a declaration that would bring unnecessary harm and economic hardship to a large segment of the chemical, construction and related industries. As you know, in my capacity as Chairman of the Subcommittee on Carcinogenesis Risk Assessment of the SAB, I have been very critical of some of the EPA-generated risk assessments based on inadequate or inconclusive data.

As a member of the Advisory Committee to the Mt. Sinai Environmental Program, I read the data then available from the CIIT Report, and I was convinced that their assays demonstrated clearly that formaldehyde was carcinogenic to rats and mice. The results I believe therefore compel an acknowledgement that formaldehyde in the gaseous state poses a risk of cancer to exposed humans.

There is general agreement among experts in chemical carcinogenesis that a substance that causes cancer in statistically significant numbers in well-conducted assays in experimental animals, by whatever route it is given and by whatever organ it affects, poses some risk to some humans. This principle is accepted worldwide and for many years has been the basis for action by regulatory agencies. It rests on a firm scientific foundation and is reinforced by unequivocal evidence that known human carcinogens are also carcinogenic when tested by well-conducted assays in experimental animals.

The assays in question were conducted in a manner considered valid by experts who examined the data, and in a laboratory supported by the chemical industry. Certain ambiguities that arose in the original assays, owing to intercurrent infections, were later resolved. Their positive results were confirmed by assays conducted at New York University. What is most significant to my mind is that the concentrations found to be carcinogenic in these assays are I understand, not far outside the range of some human chronic exposures to formaldehyde.

I well appreciate the arguments on the other side. Formaldehyde has been around a long time and some human populations have been exposed occupationally for many years without exhibiting as yet significant increases in number of cancers or in the pattern of organ susceptibility. There is as yet no evidence that exposure to polluted air, which is likely to contain formaldehyde, causes increased lung cancer. Nasal cancer, found in rats and mice exposed to formaldehyde, seems to be rare in humans. In my judgment these findings may suggest but do not yet demonstrate a minimal risk and therefore do not really outweigh the necessity to act on the basis of clear-cut assay data in animals. These assays should be a clear warning sign that possible hazards may lie ahead.

It seems to me that the agency has no choice now. Failure to declare would pit the agency against the scientific judgment of much of the country's expert opinion, and place it in an indefensible position. Criticism is already being voiced, and I would hate to see the agency subject to acute embarrassment and possible loss of credibility.

If formaldehyde is declared a potential risk to human cancer, does this have to be necessarily catastrophic to our economic well-being? Would it not be possible for the agency to take some prudent steps to minimize exposure to formaldehyde in the work place and to guard against undue exposure of the public, without excessive economic damage? Isn't there a middle road down which both the EPA and the industry could travel cooperatively, to work out solutions that could satisfy reasonable people?

As a member of the SAB, I feel I owe you these comments and I hope they are helpful and constructive. I would be happy to discuss this with you further if you wish.

With best wishes and warm regards.

Sincerely,

Sidney Weinhouse

SW:sb

CC: Terry Yosie

TEMPLE UNIVERSITY
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FELS RESEARCH INSTITUTE (215) 221-4300

May 17, 1982

Mr. Robert Nicholas, Staff Director
Subcommittee on Investigations and Oversight
Committee on Science and Technology
House Annex No. 1 Room 822
Washington, D. C. 20515

Dear Bob,

I regret very much that I will be unable to attend the hearing on May 20. During the past week I have been suffering from an acute respiratory infection and I have been hoping against hope that it would clear up in time for me to attend. A throat culture was taken last Friday and I just was informed that I have a strep infection. My doctor, Oliver Owen, at Temple, considers it very unwise for me to travel for at least this week, since I am on antibiotic medication.

Needless to say, I am sorry I cannot be with you but I am enclosing three copies of a statement which delineates my judgment with regard to the risk of human cancer posed by the experimental data.

With best wishes,

Sincerely yours,

Sidney

Sidney Weinhouse, Ph.D.

SW:daw

Enclosure

## CURRICULUM VITAE

Name: Sidney Weinhouse S.S. #211-20-1942

Date and Place of Birth: May 21, 1909, Chicago, Illinois

Education:
B.S., University of Chicago, 1933
Ph.D., University of Chicago, 1936

Positions:
1936-1938 - Eli Lilly Fellow, University of Chicago
1939-1941 - Coman Fellow, University of Chicago
1941-1944 - Wartime activities: Office of Scientific Research Development, University of Chicago
1945-1947 - Houdry Process Corporation, Head of Biochemical Research
1947-1950 - Temple University Research Institute, Biochemical Research Director
1950-1957 - Lankenau Hospital Research Institute and the Institute for Cancer Research, Head of Department of Metabolic Chemistry
1957-1961 - The Institute for Cancer Research, Chairman, Division of Biochemistry
1961-present:
Fels Research Institute, Temple University School of Medicine
Associate Director, 1961-1963; Director 1963-1976
Professor of Biochemistry, Temple University School of Medicine, 1961-1976
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Outside Professional Activities:

Present:
Member, Board of Directors, American Cancer Society (also Phila. Div.)
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  Northwestern University Cancer Center
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Former:
Chairman, Board of Scientific Counselors, National Institute of Environmental Health Sciences
Member, National Advisory Cancer Council, NIH
Member, National Advisory Council on Environmental Health Sciences, NIH
Member, Scientific Advisory Board, Damon Runyon Memorial Fund for Cancer Research
Member, Biochemistry Study Section, NIH
Member, Committee on Pathogenesis, American Cancer Society
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Honors:

Philadelphia Section Award, American Chemical Society, 1966
G.H.A. Clowes Award, American Association for Cancer Research, 1972
Doctor of Medical Science (Honorary Degree, The Medical College of Pennsylvania) 1972
Doctor of Science (Honorary Degree, Temple University) 1976
Papanicolaou Award, 1976
Japanese Association for Cancer Research (Honorary)
Lucy Wortham James Award, Society of Surgical Oncology, 1979
Doctor of Medicine and Surgery (Honorary Degree, University of Chieti, Italy) 1979
Annual National Award, American Cancer Society, 1979
Annual Achievement Award, Philadelphia Division, American Cancer Society, 1980
Member, National Academy of Sciences, U.S.A.
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Editorial Activities:

Present:

Associate Editor, Cancer Research
Co-Editor, Advances in Cancer Research
Associate Editor, Journal of Environmental Pathology & Toxicology
Associate Editor, Journal of Oncofetal Development

Former:

Editor, Cancer Research, 1969-1980
Member, Editorial Advisory Boards, Journal of Biological Chemistry; Archives of Biochemistry and Biophysics

Professional Societies:

American Chemical Society
American Society of Biological Chemists
American Association for Cancer Research
Japanese Association for Cancer Research (Honorary)
New York Academy of Sciences (Fellow)

FOR PRESENTATION AT A CONGRESSIONAL HEARING (SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT COMMITTEE ON SCIENCE AND TECHNOLOGY), MAY 20, 1982

I am a Professor of Biochemistry at Temple University School of Medicine, Philadelphia, with over 30 years experience in laboratory research on cancer. I am the immediate Past President of the American Association for Cancer Research, an organization of over 3,000 laboratory and clinical scientists; a life member of the Board of Directors of the American Cancer Society; a member of the National Academy of Sciences; and a former member of the National Advisory Council of the National Cancer Institute and the Institute of Environmental Health Sciences.

Although I understand and appreciate the reluctance to declare formaldehyde a carcinogen in view of its wide usage in the chemical, construction and related industries, I have examined the experimental data and am convinced that formaldehyde is a carcinogen in rats and probably also in mice. There is general agreement among experts in the field of chemical carcinogenesis that a substance that causes cancer in statistically significant numbers of experimental animals by whatever route it is given and by whatever organ it affects, poses some risks to some humans. This principle is accepted worldwide and rests on a firm scientific foundation. It is strongly reinforced by much evidence showing that substances known to be human carcinogens are also carcinogenic to animals when tested in well conducted assays.

The assays in question on formaldehyde were conducted in a manner considered valid by experts who examined the data, and were conducted in a respected laboratory, supported by the chemical industry, namely, the Chemical Industry Institute of Toxicology. These results were confirmed by assays conducted at the New York University Institute of Environmental Medicine. What is most impressive to me is that the concentrations found to be carcinogenic in these assays are not far outside the range of some human chronic exposures to formaldehyde.

I appreciate the fact that formaldehyde has been around a long time and some human populations have been exposed occupationally for many years without as yet exhibiting significant increases in the numbers of cancers or in the pattern of organ susceptibility. It is also true that nasal cancer found in rats and mice exposed to formaldehyde seems to be rare in humans. Epidemiologic study on humans, occupationally or environmentally exposed to formaldehyde, are urgently needed. However, this lack of epidemiologic information does not outweigh the need to urge some limitation on human exposures to formaldehyde. The experimental assays are a clear warning sign that possible hazards to humans may lie ahead.

Since the original report from the CIIT, this laboratory has published additional information which appeared in the abstracts of the 1982 meeting of the American Association for Cancer Research (p. 55, J. A. Swenberg et al.). These investigators found that formaldehyde administration caused a 10-20 fold increase in replication of cells of the respiratory system of rats and mice exposed to formaldehyde. In another paper given at the same meeting (p. 68 of the Abstracts) Grafstrom et al. demonstrated that formaldehyde caused crosslinking and strand breakage of DNA of cultured human cells of various types. The authors concluded that direct damage to DNA caused by formaldehyde as well as the inhibition by formaldehyde of DNA repair may play important roles in the possible carcinogenic or cocarcinogenic properties of formaldehyde in human respiratory epithelium.

I do not feel competent to judge the legal interpretations and consequences of a declaration on the potential risk of formaldehyde carcinogenesis in humans as set out in Section 4F of TSCA. However, I would like to comment on the conclusions in the Todhunter Report as described in pages 5 and 6. The tenor of this report suggests that if the experimental assay data indicate a risk, the epidemiologic data do not support a risk that would be of any consequence. This conclusion in my judgment is not warranted. The limited epidemiologic base is not sufficiently definitive to declare formaldehyde to be or not to be a human risk. There are no solid data to conclude that the risk to humans would be "from low priority to no concern."

I also do not agree that because of the "nature of the toxicology data and the unreliability in the exposure data one cannot reasonbly conclude, at this time that formaldehyde poses a significant risk among the U.S. population." My view is that the toxicology data are not unreliable; because exposure data are unreliable, the conclusion that formaldehyde does not pose a significant risk is unwarranted. Until firm and definitive epidemiological data are obtained to show that formaldehyde poses little or no risk to exposed humans, I think prudence requires the presumption that a potential risk exists on the basis of the clear and unequivocal experimental data.

Respectfully submitted,

Sidney Weinhouse

Sidney Weinhouse, Ph.D.

Mr. **Gore**. Taking his place is Dr. Roy Albert. We would like to extend special thanks to Dr. Albert for appearing here on quite short notice. Dr. Albert is professor of environmental medicine at NYU.

We appreciate the extra trouble that you have gone to, to come here on very short notice.

Without objection, the entire text of the witnesses' statements will be put into the record in full. We would like to invite you now to proceed, beginning with Dr. Nelson of the NYU Medical Center.

Dr. Nelson, thank you for coming. Please proceed.

## STATEMENT OF DR. NORTON NELSON, PROFESSOR, INSTITUTE OF MEDICINE, NEW YORK UNIVERSITY MEDICAL CENTER

Dr. **Nelson**. Thank you, Mr. Chairman.

In the interests of time and possibly sharpness of statement, I would like to paraphrase the points that I wish to make and have my written statement entered into the record.

Mr. **Gore**. We will do that. I think that is a good way to proceed.

Dr. **Nelson**. My name is Norton Nelson. I am professor of environmental medicine at the Institute of Environmental Medicine, New York University Medical Center, a position I have held for, I guess, nearly some 30 years. I was director of the institute for some 25 years. I have stepped aside and have been replaced by Dr. Arthur Upton, former director of the National Cancer Institute. I remain full time.

It has been my fortune, good or bad, to have lived through the sometimes tumultuous years of the development of cancer research and cancer policy relating to environmental issues in this country. I think I have been with it since the first gong was sounded and remain very actively involved at the present time.

I am currently chairman of the Board of Scientific Counselors of the National Toxicology Program, one of whose chief concerns is, of course, the issue of environmental cancer, cancer testing, and an interpretation of such cancer tests.

I was chairman of the Scientific Advisory Group of the OTA group that produced the report that the chairman commented on, "Assessment of Technologies for Determining Cancer Risks from the Environment." I have served on the special group for the National Cancer Board that produced the General Criteria for Assessing the Evidence of Carcinogenicity of Chemical Substances. I chaired a group in FDA, one of the chief activities of which was to produce protocols for cancer evaluation, and so on.

Internationally, I have been closely related to WHO in a variety of areas. I have served on a number of monograph committees of the International Agency for Research on Cancer [IARC]. I have chaired at least three or perhaps four of the monograph committees which have evaluated chemicals for their carcogenic risk.

In short, I have lived through this issue in a variety of ways, not only as a scientist directing research and involved in it myself but as a person whom the country and, I guess, the international community has called on from time to time for my advice.

My comments today, I think, will focus on the issue of principles for cancer control or cancer prevention, to a lesser degree on the science. However, the formaldehyde issue provides a very elegant tool to examine these issues, and so I will refer briefly in my statement to some of the issues relating to formaldehyde.

But I wish to emphasize the principles of cancer assessment is my basic message and relates to the following: Current cancer policy, widely accepted throughout the world, from the European Common Market to Japan—and I know these circles very, very well—to the United States of America—has been repeatedly expressed, and I think there is now a general consensus among most regulators and scientists throughout the world.

Suddenly we seem to find ourselves in a situation in which this is perhaps quietly, perhaps accurately, but not publicly, being revised.

The message I wish to convey is that surely we must review the cancer policy if it cannot stand as a valid pattern; let us then change it. But I believe that such a review should be done under not merely internal auspices within Federal agencies of this country but should be subjected to external review and debate. I will suggest some agencies which I think are quite capable of doing this, and I think that several such reviews can be carried out.

My concern derives from the fact that there is clearly a stepping back from control of what is clearly in this case a cancer agent, and so I use the formaldehyde issue to signal this point.

The problem of cancer is not as complicated scientifically as many would like to suggest that it is. Of course it is complex; of course it is difficult. We now have, however, a remarkably solid basis of science for understanding the induction of cancer from external chemicals, and the induction of cancer from radiation.

In the case of chemicals especially, we now know that we are dealing—in most cases, not all—with an injury to the DNA in the body cells producing a potentially malignant change which, under appropriate circumstances, can emerge as cancer. Once it reaches that point of unrestrained proliferation, it grows, and we are unable at this time to know how to stop that growth. This is what we call cancer.

A carcinogenic chemical can initiate a potentially malignant mutation. I may say that we now know enough to suggest that this initiation may be latent, but is not always. If latent it may be followed by promotion. Initiation is essential; to frank malignancy promotion often occurs.

Now, I would suggest to you people that the scientific complexities should not be ballooned into a basis for paralysis or for inaction. We know a great deal about chemicals causing cancer. There is a strong parallelism between the so-called Ames test and human cancer. These are powerful tests, they have been used extensively, and they have received throughout the world a large body of confidence as predicters of potential human carcinogenicity.

We should never fool ourselves into saying that a positive animal test means inevitably human cancer. Obviously, it does not. There are some exceptions to this pattern. But the proof of a human carcinogen is a very difficult matter.

Epidemiological tools are crude; they are insensitive; the groups involved must be followed for many years. They must involve a whole series of careful determinations of disease and of death and patterns of death. The epidemiological studies must be regarded as crude and insensitive tools. Only the most potent and intense carcinogens are likely to be detected by epidemiological techniques as normally conducted.

Let me give you an example. In the case of lung cancer, we are now running in excess of 100,000 deaths per year. I think it is quite possible that formaldehyde may produce lung cancer. An increase in lung cancer of 5 to 10 percent would be almost undetectable by present-day epidemiological techniques. A 5 to 10 percent increase in lung cancer is 5,000 to 10,000-plus deaths per year. This is not a socially acceptable risk.

So we must be aware that the detection by epidemiological techniques is very, very crude, and this is one factor that has led, quite simply, to the policy that we cannot wait for deaths and bodies accumulating before we have regulation.

It has been widely accepted throughout the world that positive animal studies should signal a potential danger for man.

Returning for a moment to formaldehyde—am I doing poorly on time?

Mr. GORE. Go ahead; you are doing fine.

Dr. NELSON. Formaldehyde has a chemical structure that signals cancer suspicion; that is to say, it alkylates; it reacts with organic chemicals and with DNA in a way that we know to be associated with carcinogens. Formaldehyde is positive in animal tests in several different species, in several different strains, and at dose levels that are not far from those to which people are exposed.

It is a genotoxic—that is, it produces alterations in the genetic material of the cell, as determined by direct DNA interaction and as determined by the bacterial revertant tests, such as Ames test and others.

On the basis of these considerations, one cannot debate the present scientific evidence, and this is a major message that I would like to get across. Formaldehyde is clearly an animal carcinogen. If we start from that point, what next do we do? Do we rereview, rereview, rereview, and wait until deaths occur, which are countable, some of which in fact may not be countable because they may be buried in this very large background of other sources of cancer? Or do we go into some kind of control pattern now? Obviously, my position is clear.

I have worked assiduously to suggest means for orderly scientific review of the evidence and orderly control, control that is sufficient but not excessive. This is what we need in this case; whether it is section 4(f) or not, I am not sufficiently familiar with the law as to whether that is the right form of control or not, but control is fully merited on the basis of evidence that we have today.

Again, to return to formaldehyde, I read the IARC definition which says, "Sufficient evidence of carcinogenicity, which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset." Formaldehyde meets each one of these criteria.

Indeed, IARC [the International Agency for Research on Cancer], has already acted on formaldehyde and has found the evidence "sufficient."

The points brought up in the Todhunter memorandum, which I say in my statement I find unusual and irresponsible, from the standpoint of taking a series of positions which bear in varying degrees on the carcinogenicity of formaldehyde and in each instance, contrary to accepted scientific usage, has taken a judgmental position that the evidence is insufficient—I find this inexplicable; I just cannot understand how such conclusions could have been reached.

It is clearly an animal carcinogen; it is clearly chemically eligible; it is clearly eligible from a chemical standpoint. We do not have at this time sufficient epidemiological evidence to reach a conclusion one way or the other. There has been some suggestion of nasal cancer. If nasal cancers are found in humans, that will be very persuasive evidence. I am not personally acquainted with those data.

However one should not assume that there must be total concordance between animal tests and human outcome in that cancers in the same organ are essential for relevance. We have many examples in which the animal tests have predicted a severe danger of cancer, and which was positive in humans, yet produced cancer in a different organ in animals than that found in humans.

Accordingly, what I find here is a major alteration in the judgmental evaluation of evidence which in the last decade has been found acceptable by society and which is generally and widely regarded as adequate to move in the direction of control. The alternative of waiting until human evidence has accumulated is obviously irresponsible, insupportable, and inhumane.

I come back therefore to the suggestion that a rereview of cancer policy is in order. I would strongly recommend that it be done.

I put before you at least three agencies that I believe would be highly competent to undertake such a review. One of these would be the National Academy of Sciences/National Research Council with which I have been long associated and guided many of their studies; a second option is the National Cancer Board through an appropriate subcommittee which I worked with at an earlier time. Third I believe that the Board of Scientific Counselors of the National Toxicology Program would be willing, if asked, to put together a panel to carry out such a review of cancer policy.

We did something like this in the OTA document that you referred to, Mr. Chairman, so the rereview is not all that ancient. That was 1½ or 2 years ago.

Nevertheless, I think this issue has been again signaled as important and one that arouses concern and apprehension. These are sufficient, in my view, to justify at least one formal public review of cancer policy.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Nelson follows:]

# TESTIMONY BEFORE THE SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT OF THE COMMITTEE ON SCIENCE AND TECHNOLOGY

My name is Norton Nelson. I am Professor of Environmental Medicine in the Institute of Environmental Medicine, New York University Medical Center. I was Chairman of the Department and Director of the Institute of Environmental Medicine for some 25 years, a position which I relinquished some two years ago. I have been succeeded by Dr. Arthur Upton, former Director of the National Cancer Institute. I, however, remain full time in teaching and research in the Institute.

A long career in environmental health has included the involvement of perhaps half of my time, and of the Institute's, in issues relating to environmental cancer. Accordingly, I have been intimately related to the development of the knowledge base in this extremely interesting field for many years and, because of that involvement, have actively participated in many advisory roles in this country and internationally in environmental cancer. I will not cite all of these, which would be tedious and boring to all of us. I might merely say that over the years I have been continuously involved in a series of advisory roles to the National Cancer Institute; these included The Clearinghouse on Environmental Cancer, as a consultant to the National Cancer Board Panel on Environmental Cancer, which produced a document called "General Criteria for Assessing the Evidence of Carcinogenicity to Chemical Substances," and many other advisory relationships to NCI. I have been continuously related to the program of the National Institute of Environmental Health Sciences which has had a strong interest in environmental cancer since its inception. I chaired the Food and Drug Administration Committee on Protocols for Safety Evaluation, one of the chief activities of which was the production of a document on cancer testing. I served on the Science Advisory Board of EPA from its organization until last October and was Chairman of its health committee throughout that period. I have been intermittently (and am currently) a member of the Armed Forces Epidemiological Board, which is frequently concerned with the problems of occupational and environmental cancer. I served on a special committee to the Office of the Secretary of HEW in which I chaired the committee which led to the establishment of the National Center for Toxicological Research. I am currently serving on a committee advisory to the Secretary of HHS relating to Agent Orange. I served on a series of advisory groups to the Office of Science and Technology and the President's Science Advisory Committee over several administrations. Many of the issues concerned were environmental cancer. I served on a White House panel on air pollution which dealt with the problems of air pollution cancer amongst other issues. I have served for many years on advisory committees to the National Academy of Sciences/National Research Council and was first Chairman of the Board on Toxicology and Environmental Health Hazards which is regularly concerned with problems of environmental cancer. A little over a year ago I chaired the Scientific Advisory Committee to the Congressional Office of Technology Assessment, which led to the report, "Assessment of Technologies for Determining Cancer Risks from the Environment."

Internationally, I have worked for many years with WHO in a variety of committee and special advisory roles. I have also been closely associated with the International Agency for Research on Cancer (IARC), which produces the widely accepted monographs on the evaluation of cancer from environmental and other sources. I have chaired a number of the monograph committees which have produced those reports as well as committees reviewing other aspects of IARC's program. There are other similar activities, but these may establish a long involvement in the field of environmental cancer.

In my comments today I would like to state my concern about what I see as an alarming tendency towards a change in the national policy for regulating carcinogens which, unless examined, may go beyond prudent public health policy and good science. My apprehensions may be incorrect; I hope they are. I understand that there is underway in OSTP a re-review, as there should be periodically, of national cancer policies relating to environmental chemicals. I wish them well and await their deliberations. I will further suggest below that in addition to this "in house" review, other more "public" reviews should be undertaken. Until these reviews are completed, debated, and accepted, I believe we should stay with present policy.

In my remarks I would like to speak rather generally about principles which have emerged over the last ten to fifteen years relating to cancer policy and express my opinion as to their current relevance and validity. In doing so I will on occasion call attention to the current controversy over formaldehyde since that provides an up-to-date issue on which there have been official pronouncements, and which has added to my concern that cancer policy may be under major revision. It is true that our Institute at New York University has been intimately involved in tests relating to formaldehyde; however, that is not my primary reason for using this as a focus for the discussion. Other agencies have also carried out tests on formaldehyde, and the basic science is not really controversial at this stage.

Society is, for very persuasive reasons, concerned about chemical carcinogens (that is, chemicals that cause cancer) that may potentially expose either special groups (as in occupations) or, in general, consumers. Cancer is a disease that is often irreversible, often fatal; once initiated, it cannot, at this time, be halted with certainty; the only known totally reliable method of prevention is to avoid exposure. Most chemical carcinogens, although not all, act by producing genetic alterations in the cells of the body, the somatic cells, so that they can still reproduce as cells but, in doing so, will lead to aberrant and uncontrolled growth; this is what we call cancer. Our understanding of the biology of this process has improved immensely over the last ten years so that, at this time, we have a rather coherent pattern of understanding of these events; these are rather generally accepted by the scientific community. That is not to say that there is not debate over many aspects. Nevertheless, this general concept is very widely accepted as an approximate description of the means whereby normal cells can become malignant and lead to uncontrolled growth when exposed to chemical carcinogens.

In recent years there has been developed an elaborate pattern of testing chemicals for carcinogenicity (often pretesting before use) through the use of laboratory studies which generally extend over the lifetime of the animals. In most cases these tests are carried out on rats or mice.

More recently there has been developed a very powerful tool based on mutagenicity tests in isolated systems such as bacteria. This development is largely due to Professor Ames of the University of California at Berkeley. These tests are very powerful, especially in their ability to measure the kinds of mutations relevant to cancer induction. However, neither the animal tests nor the bacterial tests are wholly reliable; both have their defects as well as their power. The animal tests have been almost totally successful in duplicating human experience in some thirty known substances that are carcinogenic to humans. The two holdouts in this success story, arsenic and benzene, may now be giving answers which will eliminate them as resistant to animal test. The bacterial revertant tests have a very good correlation in terms of their predictivity for a malignant outcome. At the present time the animal tests (for obvious reasons) are regarded as the more definitive.

In these and my following comments I will in some cases not reference certain statements of principle. If it is the desire of the Committee, I will be glad to try to supply the appropriate citations; but I believe that anyone in the field will recognize the widespread acceptance of the principles that I will comment on.

First, a well-documented positive outcome in a lifetime test on mammals should be accepted as potentially capable of producing cancer in humans. In the IARC definition, this fits the category of "sufficient" evidence; their definition is as follows:

> "Sufficient evidence of carcinogenicity, which indicates that there is an increased incidence of malignant tumours: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset."

Only one of these criteria needs to be met; yet the formaldehyde data meets this requirement in respect to (a), (b) and (c).

This is in decisive contrast to the statement in the memorandum of Dr. Todhunter of EPA through Dr. Hernandez to Administrator Gorsuch dated February 10, 1982, which states that "tests on a chemical compound are 'significant' when it is carcinogenic in at least two species tested and all sexes in these species."

IARC has evaluated the animal data on formaldehyde and found it "sufficient," as have many other agencies.

It is also widely recognized that certain chemical properties, particularly the alkylating ability of an agent, lend additional evidence to the probability of carcinogenicity. Formaldehyde is such an agent. Formaldehyde is also mutagenic in the bacterial systems earlier described.

The IARC warning when evidence for the carcinogenicity of a chemical is "sufficient" is as follows: "In the absence of adequate data in humans, it is reasonable for practical purposes to regard such chemicals as if they presented a carcinogenic risk to humans."

Let us now consider the case of formaldehyde in the light of our simplified set of principles relating to non-human evidence of the carcinogenicity of formaldehyde: (1) formaldehyde is in a class of chemical compounds likely to have the kind of reaction with DNA associated with carcinogenic agents; (2) this is in fact confirmed in mutagenicity studies in bacterial short-term systems; (3) positive outcomes have been secured in two different laboratories at several dose levels and in several species. These laboratory tests thus clearly meet criteria widely accepted in this country and abroad as confirming the carcinogenicity and mutagenicity in non-humans of this chemical.

Yet, the Todhunter memorandum concludes that the evidence is not fully adequate to meet the designation "significant."

I might parenthetically add that the Todhunter memorandum is in some ways a remarkable document which goes through a series of biological issues, point by point, some highly relevant, some less relevant, and in each case concludes that in the judgment of the writer of that memorandum, the evidence does not merit the regulation of formaldehyde under EPA legislation. I say the document is remarkable in the sense that in each issue examined, an extreme position is taken relating to the probable non-significance of the data on formaldehyde. It would perhaps be understandable for such an analysis to be prepared by industry or a manufacturing firm using formaldehyde. To be put forward as a dispassionate examination of evidence by a public agency responsible in this country for protecting the health of the public from such agents must be viewed as irresponsible. Obviously, such an evaluation clearly violates the principles which have been promulgated and widely accepted as based on a prudent concern for protecting the health of the public.

The point is made in the Todhunter memorandum that tumor correspondence in humans with those organ sites found in laboratory studies is essential. This is far from being the case; there are many examples in which a positive outcome in one organ in animals has been predictive of a positive outcome at another organ site in humans. In the instance of formaldehyde, the implication has to do with the finding of nasal cancer in the two major laboratory studies using rodents, and therefore, he implies, one should only be concerned with nasal cancer in humans. One should, of course, look for nasal cancer in humans; however, the possible production of lung cancer or other cancer (especially skin) in humans from formaldehyde can by no means be eliminated. Certainly the nose is efficient as a remover of formaldehyde, yet some formaldehyde may well reach the trachea and bronchi in humans. In fact, humans do a great deal of breathing through the mouth where access to the deeper parts of the respiratory system would be much more likely than they would be in rodents which are obligatory nose breathers.

I will only very briefly comment on the implied EPA policy suggesting that in the absence of confirmed epidemiological data, the likelihood of human carcinogenicity cannot be accepted. This position requires comment at several levels. First, it is unquestionably true that in the absence of cancer in humans directly traceable to a chemical, the human carcinogenicity of that chemical cannot be proven, and the term proven should be underlined. All thoughtful people will recognize this as a simple statement of logic; however, all thoughtful and responsible persons will also accept the position which I have briefly outlined as a basis for using laboratory tests as a prudent policy for protecting the health of the public. The high predictability of animal tests and the good, but not so high, predictability of bacterial revertant tests should leave no doubt in the mind of any reasonable person. For any agency, person or industry to insist that positive cases of cancer in humans must be proven before regulation is undertaken is a truly irresponsible and insupportable position to take.

In the discussion of the carcinogenicity of formaldehyde, much has been made of the irritant properties of formaldehyde. This is a red herring in which the implication is that irritancy was crucial to the development of carcinogenicity. In our studies at NYU in rats exposed both to formaldehyde and hydrochloric acid (HCl), a known very potent irritant, no greater increase in cancer was observed than in rats exposed to formaldehyde alone, nor was cancer found in any of the animals exposed to HCl alone.

Another issue which can be raised, and is raised in Dr. Todhunter's memorandum, is the question as to whether a particular agent is an initiator or a promoter. Whether chemicals operate primarily as initiating or promoting agents, some degree of control is likely to be required.

In the particular case of formaldehyde, there can be little doubt that formaldehyde is an initiator since it is genotoxic; that is, it produces DNA damage and genetic alterations, so that it is almost certainly an initiator. It may also be a promoter; such an additional characteristic is not decisive for current public health control purposes.

Epidemiological data showing a positive association between exposure to a chemical and an unusual occurrence of cancer would, of course, cap the evidence and leave little uncertainty as to a causal relationship. However, the absence of a positive outcome by no means proves that human cancer is not occurring. In general terms, epidemiological studies are difficult and very insensitive; they are difficult in establishing evidence as to the extent of exposure. This is especially true in cancer studies since there is generally a long latent period between exposure and the occurrence of cancer and a definitive outcome generally requires a very substantial excess of cancer, especially if the lesion is a frequent one, as is the case with lung cancer. Valid epidemiological studies normally require study of a large group of exposed persons over a lengthy period of time and, as well, a definitive determination of the fate of the exposed population. These requirements are very difficult to fulfill. Epidemiological studies must be regarded as relatively crude and relatively insensitive. Therefore, a negative outcome, unless unequivocally rigorous, can by no means be regarded as exonerating a suspect agent.

In the case of formaldehyde, the studies so far conducted do not meet the requirements of exonerating formaldehyde; they must simply be regarded as inconclusive at this stage. There have been reports of a series of nasal cancers occurring in formaldehyde exposed persons; if an increased incidence of these tumors is in fact validated and exposure is confirmed, this would be quite decisive evidence of an association since nasal cancer is very rare in humans. However, my personal knowledge of these cases and their background is too scanty for me to comment on them at this time.

At one point Dr. Todhunter, in commenting on risk assessment, notes that certain levels of cancer are probably undetectable against the background of the normal occurrence of cancer. This is an issue which I think needs to be signaled. It is certainly true that the occurrence of an increase in lung cancer will be very difficult to detect because lung cancer has a high normal frequency, especially in smokers. A five or even a ten percent increase in lung cancer would be very, very difficult to detect epidemiologically. Nevertheless, a five or ten percent increase in lung cancer would correspond to something like 5,000 or 10,000 additional deaths. Five thousand or 10,000 additional deaths can hardly be regarded as inconsequential to society. On the other hand, a rare tumor such as a nasal cancer has a low background, and a positive outcome there would be comparatively easy to detect, as perhaps in fact they have been detected.

The point to be made here is that detectability should never, under any circumstances, be grounds for disregarding a cancer risk. It is the absolute impact, not the percentage or relative impact, that society needs to be concerned with. Again, in this sense epidemiology is a crude tool for measuring social impacts which are nevertheless important.

Let me say a few words about thresholds which also receive extensive discussion in Dr. Todhunter's memorandum. In his memorandum there is the implication that there may be, and perhaps are, thresholds for formaldehyde which would make human exposures to lower levels negative and inconsequential. This cannot be accepted without comment. In the first place, the usual studies using laboratory animals with groups of manageable size are relatively insensitive for measuring dose response relationships, and are normally quite incapable of detecting thresholds. It is very chancy to attempt to depend exclusively on such data for estimating the risk to humans. I am in favor of using quantitative risk assessments, but such use must be done judiciously and with a clear recognition of quantitative limitations; our science is simply not skilled enough to permit precise estimates of risk in these instances. In addition, the assumption of the threshold is widely regarded in the scientific community as being an imprudent assumption for public health protection. The basic issues are rather simple. The demonstration of a threshold in animal studies would be a feat of major proportions, extraordinarily difficult, expensive, and of uncertain outcome. The closest approach to such an attempt was a very elaborate, large scale study at NCTR in which interpretation of the data would perhaps permit a conclusion of a possible threshold with bladder cancer occurrence, but not with liver cancer. However, these studies, although suggestive, cannot be regarded as definitive. We must accept the fact that a demonstration of a practical threshold in humans or in animals is likely to be difficult and elusive and, at the present time, probably not attainable.

Any biologist working in these fields can dream of several scenarios describing biological action of carcinogens which would postulate the presence of a threshold. And there may well be practical thresholds for some chemicals. On the other hand, there are even more persuasive biological grounds for thinking that in many cases, perhaps the great majority, there will be no threshold. Since the practical demonstration of a threshold is difficult, often impossible, a prudent course for purposes of public health control is to assume that there is no threshold.

In conclusion, I would say that I would strongly support a review of cancer principles related to the use and interpretation of scientific evidence in the control of environmental cancer. It should be noted that such a review for Congress was recently completed by the Office of Technology Assessment. The review under OSTP is underway and, of course, it should be continued and completed. I would strongly recommend that the National Academy of Sciences/National Research Council be asked to undertake a review. Another eligible body would be the Board of Scientific Counselors of the National Toxicology Program. It is perfectly appropriate for these issues to be periodically raised, on the one hand, to make changes where these are indicated and, on the other, to reassure ourselves that previous positions are still valid where that is in fact the case.

Thank you.

Mr. **Gore**. Thank you very much for an excellent statement.

We will have a number of questions for you, but we will hold off until the other members of the panel have completed their statements.

Dr. Roy Albert, professor of environmental medicine at NYU Medical Center, would you go next, please?

Without objection, your entire statement will be put in the record. If you care to summarize, that will be fine with us. You proceed as you see fit.

## STATEMENT OF DR. ROY ALBERT, PROFESSOR OF ENVIRONMENTAL MEDICINE, NEW YORK UNIVERSITY MEDICAL CENTER

Dr. **Albert**. I have a short statement which I would like to read.

My name is Roy Albert. I am professor of environmental medicine at the New York University Medical Center, where I am deputy director and vice chairman of the Institute of Environmental Medicine. I have been trained in medicine and have devoted my career to teaching and research. My primary research is in the field of environmental cancer and includes a demonstration of the carcinogenicity of formaldehyde by inhalation in rats which was published last month in the journal of the National Cancer Institute.

In addition to my affiliation with New York University, I have been associated with the Environmental Protection Agency since 1975. From 1975 to 1976 I was the Deputy Assistant Administrator for Health and Ecology in the EPA on leave from NYU. At that time I was given the responsibility for formulating the EPA's approach to carcinogen risk assessment as chairman of an internal EPA committee with external participation by distinguished scientists from various parts of the country.

This policy was adopted and published in the Federal Register in May 1976, and since 1976 I have been chairman of the EPA's Carcinogen Assessment Group, which has had an agencywide oversight role to insure the quality and consistency of the EPA's risk assessment. I am still chairman of the Carcinogen Assessment Group.

I am speaking from two perspectives: As a member of the academic community and as someone associated with EPA's scientific assessment activities. I am testifying here as a private individual, and I was not involved with the formaldehyde risk assessment that is under discussion here.

I believe that the memorandum by Dr. John Todhunter to Administrator Gorsuch dated February 10, 1982, in support of the decision not to list formaldehyde under section 4(f) of the Toxic Substances Act reflects a serious flaw in the EPA's administrative processes.

The EPA has elaborate review procedures involving its in-house scientists as well as its Science Advisory Board for scientific documents which are developed in support of regulatory action. In sharp contrast, the EPA has no such review procedures for documents which are developed to support a decision not to regulate.

For example, in the last administration, the Office of Toxic Substances issued a document effectively permitting the reintroduction of nitrilotriacetic acid for use in detergents in this country. This document was not subject to agency or SAB [Science Advisory Board] scientific review.

I am reasonably sure that the February 10, 1982, Todhunter formaldehyde document was not reviewed by scientists within the EPA or the Science Advisory Board. All of the faults of this document, I believe, can be ascribed to the short circuiting of the scientific review process.

The Todhunter formaldehyde document was written in support of a regulatory decision. The exposition of the science was clearly tailored to fit the decision. The document is far too one-sided to be regarded as a balanced assessment of the cancer risks from formaldehyde.

It is only proper that political factors be taken into account in making regulatory decisions, since regulatory action can have substantial social impact. However, it is absolutely essential to the soundness of regulatory decisions that their underlying scientific assessments of health risks be shielded from the political forces that operate at the level of the regulatory offices.

This objective can be accomplished in two ways: One, to keep the responsibility for the scientific health risk assessments out of the regulatory offices in the EPA; and, two, to have all risk assessment documents, whether in support of regulatory action or regulatory inaction, be subject to rigorous scientific review by scientists within and outside the Agency.

This is a simple, straightforward remedy to a chronic problem within the EPA that transcends personalities and administration. I believe that Congress can be instrumental in effecting this needed change.

Thank you.

Mr. GORE. Thank you very much.

We would like to call next on Dr. Kenny Crump, president of Science Research Systems, Inc., in Ruston, La.

## STATEMENT OF DR. KENNY S. CRUMP, PRESIDENT, SCIENCE RESEARCH SYSTEMS, INC., RUSTON, LA.

Dr. CRUMP. Thank you.

I have a written statement which I would like to be entered in the record, and I would like to paraphrase that statement at this time.

My name is Kenny Crump. I live at 1628 Hodges Road, Ruston, La. I have a Ph. D. degree in mathematics. I have conducted research, which has been published in scientific journals dealing with statistical issues related to environmental data, with the properties of dose response curves for carcinogens, and with the assessment of human health risks using animal bioassay data or human epidemiological data.

I now work full time in consulting and research, specializing in analysis and interpretation of health and environmental data.

I have developed or assisted in developing several statistical extrapolation procedures for estimating risks from low doses of carcinogens which use data gathered in much higher doses. One of these procedures—the linearized multistage method—has been used by EPA in conducting risk assessments for a number of carcinogens.

It was stated in the Todhunter memo on formaldehyde that this procedure was used to make the estimates of cancer risk contained in that document. In extrapolation procedures such as this, a mathematical model is fit to animal bioassay data, and the fitted model is used to predict the probability of cancer at doses below those for which significant increases in cancer were observed in the experiment.

Statistical procedures are used in combination with the mathematical model to obtain upper limits on lifetime cancer risk at low doses. Extrapolation procedures such as this are necessary because of the difficulty in estimating small increases in cancer risk from data on a limited number of animals.

For example, the PRL-1 document cited in the Todhunter memo lists no tumors out of 160 animals in the CIIT rat bioassay of formaldehyde from a dose of 2.1 ppm. This does not imply, however, that a dose of 2 ppm carries no tumor risk.

If the true risk were 2 percent, tumors would be observed in 160 animals only about 95 percent of the time. In other words, 2 percent is a 95 percent upper confidence limit on the risk at 2 ppm. Statistical extrapolation procedures can be used to predict the risk at doses such as 2 ppm for which the increased risk cannot be accurately measured because of limitations of sample size.

It has been noted by many investigators that the outcome of an extrapolation can depend, to a considerable extent, on the mathematical dose response model used in the extrapolation.

I previously made an argument for the point of view that carcinogens which initiate cancer by causing an inheritable change in DNA, it might be expected that at low doses the increases in carcinogenic risk is linear in dose or, in other words, simply proportional to the dose. Formaldehyde, because it is a mutagen, would be suspected of being a carcinogen of this type.

The linearized multistage extrapolation procedure which was used for the risk assessment in the Todhunter memorandum has this linear property at low doses. However, the multistage model itself is flexible and able to fit nonlinear data such as the formaldehyde data, and it does fit those data.

I consider upper statistical confidence limits on risks computed using this approach to be "plausible upper limits" on the true risk. It seems unlikely that the risk is much larger than that predicted by these limits. If the true dose response is nonlinear at low doses, these upper limits might overestimate the true risk by a considerable amount.

Using this multistage approach, the upper limits on risks corresponding to a dose of 1 ppm of formaldehyde is 1.8 times 10 to the −3.

The technical document upon which the Todhunter memorandum may have been partially based used a slightly different set of tumor data, and these data yield a 95 percent upper limit of 1.7 times 10 to the −3. Therefore, the difference in the estimates from these two data sets appear negligible.

At this time I have not had an opportunity to analyze the tie-in to tumor data. However, based upon the descriptions of experimental results which I have read, I do not expect the tie-in to tumor analysis would produce risk estimates which differ substantially from those made from the data which I have seen.

The particular multistage model which provides the best fit to the data yields estimates of risk which can be considerably smaller than the 95 percent upper limit. These estimates are called MLE's by statisticians.

However, MLE's have a large variability, and for this reason I feel that generally they do not provide a suitable basis for regulatory decisions. For example, if only a single animal in the 2.1 ppm dose group had had a tumor, the MLE estimate of risk at a dose of 0.1 ppm would have been larger by a factor of 100.

I would therefore use the 95 percent upper confidence limit as a plausible upper limit for the risk, with the realization that the risk could be much less if the true dose response model were nonlinear at low doses.

It is common practice for the Carcinogen Assessment Group of the EPA to present 95 percent upper limits but not MLE's.

The details of the risk assessment procedures used in the Todhunter memorandum are not clearly described, and I have not been able to reproduce the risk estimates made in this document. When I used the assumptions that are described in the document, I got larger estimates of risk.

The Todhunter memorandum indicates that the estimates are based upon representative "median or average exposure estimates." It is also indicated in the Todhunter memorandum that "relative risks are calculated and expressed as 95 percent upper confidence limits on lifetime risks."

Using these assumptions, I have not been able to reproduce risk estimates which approximate those in table 4 of the Todhunter memorandum. Consider, for example, residents exposed to U-F foam. The Technical Document lists about 1.4 persons so exposed. Using the methodology described in the Todhunter memorandum, I calculate a lifetime risk for this group which is between 10 to the −4 and 10 to the −3.

On the other hand, table 4 of the Todhunter memorandum estimates only 580,000 persons with risks above 10 to the −4. Further, the Technical Document lists a midpoint ambient U.S. exposure of .01 ppm. Applying the methodology described in the Todhunter memorandum to this exposure yields a risk to the general population from ambient exposures of slightly greater than 1 in 10,000.

Therefore, it is problematic whether persons exposed to only ambient levels belong in the 1 in 1 million, to 1 in 10,000 or in the 1 in 10,000 to 1 in 1,000 category. In the Todhunter memorandum these persons were placed in the 1 in 1 million to 1 in 10,000.

Dr. CRUMP. Assuming that the .01 ppm actually reflects the median exposure in the U.S. population, this would correspond, using the methodology described in the Todhunter memorandum, to a median risk of 1 in 10,000.

Consequently, if this is a median risk, you would expect, on that basis, about half the people in the United States would have a risk estimated on this basis corresponding to greater than 1 in 10,000.

That concludes my comments. Thank you.

[The prepared statement of Dr. Crump follows:]

Testimony by

Kenny S. Crump, Ph.D.

before the

Subcommittee on Investigations and Oversight
Committee on Science and Technology
U.S. House of Representatives

concerning the Environmental Protection Agency's carcinogenic risk assessment of formaldehyde

May 20, 1982

My name is Kenny S. Crump. I live at 1628 Hodges Road, Ruston, Louisiana. I received a Ph. D. degree in Mathematics from Montana State University in 1968. From 1968 to 1970 I was Professor of Mathematics and Statistics at Louisiana Tech University. During this time I spent one year as a Visiting Scientist at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina. I also served as principal investigator of research grants or contracts from the National Institute of Arthritis, Metabolism and Digestive Diseases; National Institute of General Medical Sciences; and National Institute of Environmental Health Sciences. I have a number of publications in scientific journals dealing with the properties of dose response curves for carcinogens and with the assessment of human health risks using animal bioassay data or human epidemiological data. I am also the author of several chapters of books dealing with these issues. For the past two years I have served as president of Science Research Systems, Inc., a firm which I founded and which specializes in the analysis and interpretation of health and environmental data.

I have developed or assisted in developing several statistical extrapolation procedures for estimating risks from low doses of carcinogens using data from much higher doses. One of these procedures--the "linearized multistage method" (Crump, 1982)--has been used by EPA in conducting risk assessments for a number of carcinogens. It was stated in the Todhunter memo (TM) on formaldehyde and DEHP (EPA, 1982) that this procedure was used to make the estimates of cancer risk contained in that document. In such extrapolation procedures as this, a mathematical model is fit to animal bioassay data and the fitted model is used to predict the probability of cancer at doses below those for which significant increases in cancer were observed in the experiment. Statistical procedures are used in combination with the mathematical model to obtain upper limits on lifetime cancer risk at low doses and lower limits for the dose producing a given level of increased risk. Extrapolation procedures are necessary because of the difficulty in estimating small increases in cancer risk from data on a limited number of animals. For example, the PRL-1 document cited in the TM lists the following data from the CIIT rat bioassay of formaldehyde:

| Dose(ppm) | 0 | 2.1 | 5.6 | 14.1 |
|---|---|---|---|---|
| Response | 0/160 | 0/160 | 3/160 | 95/190 |

The entry 3/160 indicates that tumors were discovered in 3 out of a total of 160 animals tested, etc. Note that no tumors were found in the 160 animals dosed at 2 ppm. This dose not imply, however, that a dose of 2 ppm carries no tumor risk. If the true risk was 0.02, tumors would be observed in 160 animals only about 95% of the time. In other words, 0.02 is a 95% upper confidence limit on the risk at 2 ppm. Statistical extrapolation procedures can be used to predict the risk at doses such as 2 ppm for which the increased risk cannot be accurately measured because of limitations in sample size.

It has been noted by many investigators that the outcome of an extrapolation can depend to a considerable extent on the form of the mathematical dose response model used in the extrapolation; different models can all fit the experimental data about equally but yet predict very different risks at low doses. I have previously made an argument (Crump et al., 1976) for the point of view that for carcinogens which initiate cancer by causing an inheritable change in DNA, it might be expected that at low doses the increase in carcinogenic risk is linear in dose or, in other words, simply proportional to the dose. Formaldehyde, because it is a mutagen, would be suspected of being a carcinogen of this type.

The linearized multistage extrapolation procedure which was used for the risk assessment in the TM has this linear property at low doses. However, the multistage model itself is flexible and able to fit nonlinear data such as the formaldehyde data listed above. I consider upper statistical confidence limits on risk computed using this approach to be "plausible upper limits" on the true risk. It seems unlikely that the risk is much larger than that predicted by these limits. If the true dose response is nonlinear at low doses, these upper limits might overestimate the true risk by a considerable amount. However, the linearized multistage approach does not give the largest risks of any of the well-known extrapolation models. For example, the one-hit procedure which previously was often used by EPA frequently predicts larger risks than the linearized multistage method.

The multistage model provides an excellent fit to the formaldehyde data listed above. The expected numbers of tumors estimated from the model are as follows:

| Dose (ppm) | Observed | Expected |
|---|---|---|
| 0 | 0 | 0 |
| 2.1 | 0 | 0.35 |
| 3.6 | 3 | 6.5 |
| 14.1 | 95 | 92 |

The 95% upper confidence limit on risk corresponding to a dose of 1 ppm is $1.8 \times 10^{-3}$[a]. Because of the linearity of these upper confidence limits to obtain 95% upper limits for other animal doses, one simply multiplies the dose in ppm by $1.8 \times 10^{-3}$. For example, the 95% upper limit on risk from 0.1 ppm is $0.1 \times 1.8 \times 10^{-3} = 1.8 \times 10^{-4}$.

The particular multistage model which provides the best fit to the data yields an estimate (called a maximum likelihood estimate or mle by statisticians) of risk from 0.1 ppm of $2.4 \times 10^{-7}$ which is considerably smaller than the 95% upper limits. However, mle's have a large variability and for this reason I feel that generally they do not provide a suitable basis for regulatory decisions. For example, if only a single animal in the 2.1 ppm dose group had had a tumor, the mle estimate of risk for a dose of 0.1 ppm would have been larger by a factor of 100. I would, therefore, use the 95% upper confidence limit as "plausible upper limits" for the risk with the realization that the risk could be much less if the true dose response model were nonlinear at low doses. It is common practice for the Carcinogen Assessment Group of the EPA to present 95% upper limits, but not mle's.

The details of the risk assessment procedures used in the TM are not clearly described and I have not been able to reproduce the risk estimates from this document. When I use the assumptions that are described in the TM, I get larger estimates of risk. Table IV in the TM gives estimates of the numbers of people whose risks from formaldehyde lie in ranges of $10^{-6}$-$10^{-4}$, $10^{-4}$-$10^{-3}$, $10^{-3}$-$10^{-2}$, and greater than $10^{-2}$. The TM indicates that these estimates are based upon "representative (median or average) exposure estimates." It is also indicated in the TM that "relative risks are calculated and expressed as 95% upper confidence limits on lifetime risks." Using these assumptions I have not been able to reproduce risk estimates which approximate those in Table IV. Consider for example residents exposed from U-F foam. The EPA Technical Document (TD) lists 1,330,000 - 1,560,000 persons so exposed. The exposure estimates range from 0.05 ppm to 3.40 ppm and exposure duration from 100 to 150 hours per week for five years. A footnote to Table IV in the TM lists a median exposure of 0.72 ppm. Using this median exposure, I calculate a lifetime risk of

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[a] The EPA Technical Document upon which the TM may have been partially based used a slightly different set of tumor data. These data yield a 95% upper of $1.7 \times 10^{-3}$. Therefore the difference in the estimates from the two data sets appears to be negligible. At the time of this writing I have not had an opportunity to analyze the time-to-tumor data. However, based upon the descriptions of the experimental results which I have read, I do not expect a time-to-tumor analysis would produce risk estimates which differ substantially from those made from the data listed earlier.

$$(1.8\times10^{-3}\text{ppm}^{-1})(0.72\text{ ppm})\left(\frac{125\text{ hrs/week}}{30\text{ hrs/week}}\right)\left(\frac{5\text{ years}}{70\text{ years}}\right) = 4\times10^{-4}$$

The term $1.8\times10^{-3}$ $\text{ppm}^{-1}$ is the 95% upper limit on carcinogenic potency estimated from the multistage model, the factor 125/30 accounts for the fact that humans are exposed in homes for an average of 125 hours per week whereas the experimental animals were exposed for 30 hours per week, and the factor 5/70 accounts for the fact that these persons will be exposed for 5 years out of an expected 70 year lifespan. The TD also estimates that 2,200,000 residents are exposed to formaldehyde from plywood or particle board in mobile homes. Estimates of these exposures range from less than 0.03 ppm to 2.54 ppm, and the TM lists a median exposure for this group of 0.4 ppm. Using the median exposure using the same assumptions as were used for U-F foam exposures, I obtained a lifetime risk estimate of $2x10^{-4}$. Therefore these two groups alone contain $2.2x10^{6} + 1.4x10^{6} = 3.6x10^{6}$ persons with risks estimated from $10^{-4}$ to $10^{-3}$. Table IV of the TM, on the other hand, estimates only $5.8x10^{5}$ persons with risk above $10^{-4}$. Further, the TD lists a midpoint ambient U.S. exposure of .01 ppm. Applying the previously described methodology to this exposure yields a risk to the general population from ambient exposures of slightly greater than $10^{-4}$. Therefore it is problematic whether persons exposed to only ambient levels belong in the $10^{-6}$ to $10^{-4}$ risk or the $10^{-4}$ to $10^{-3}$ category. In the TM these persons were placed in the $10^{-6}$ to $10^{-4}$ category.

On page 14 of the TM, it is suggested that since there was no difference statistically between the 5.6 ppm response and the zero responses at 0 ppm and 2.1 ppm, it might be appropriate to treat this response as a zero also for purposes of risk assessment. I can think of no valid reason, from a statistical perspective, of making such an adjustment to the data. Indeed, because nasal tumors occur spontaneously with such a low frequency in these animals, the nasal tumors which occurred at 5.6 ppm are particularly significant.

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EPA (1982). Memorandum from John A. Todhunter to Ann Gorsuch on the subject: Review of Data Available to the Administrator Concerning Formaldehyde and di(2-ethylhexyl) Phthalate (DEHP).

# CURRICULUM VITAE

## Kenny Sherman Crump

Date of birth: October 13, 1939
Place of birth: Haynesville, Louisiana
Marital Status: Married
Children: Three

### Education

| | | |
|---|---|---|
| 1961 | B.S. Electrical Engineering | Louisiana Tech University |
| 1963 | M.A. Mathematics | University of Denver |
| 1968 | Ph.D. Mathematics | Montana State University |

### Honors

B.S. cum laude, Omicron Delta Kappa, Phi Kappa Phi, Tau Beta Pi, Eta Kappa Nu, Who's Who in American Colleges and Universities, Engineering Honor Freshman, Louisiana Tech Sigma Xi Research Award-1977, Sigma Pi Sigma.

### Major Research Interest

Application of statistics and stochastic processes to problems in biology and health.

### Professional Society Memberships

American Statistical Association
Institute of Mathematical Statistics
Biometric Society
Sigma Xi, The Scientific Research Society of North America
Society for Epidemiologic Research
American Association for the Advancement of Science

### Professional Experience

| | |
|---|---|
| 1961-1963 | Research Associate, Denver Research Institute |
| 1963-1966 | Instructor of Mathematics, Montana State University |
| 1966-1980 | Professor of Mathematics and Statistics, Louisiana Tech University |
| 1967-1968 | Research Associate, Department of Statistics, State University of New York at Buffalo (on leave) |
| 1969 (summer) | Research participant, Statistics group, Mathematics Section, Oak Ridge National Laboratory, Tennessee |
| 1974-1975 | Visiting Scientist, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina (on leave) |
| 1978-present | President, Science Research Systems, Inc. Ruston, Louisiana |

## Other Professional Activities

### A. Research Grants and Contracts

| | |
|---|---|
| 1974-1977 | Principal Investigator, National Institute of Arthritis, Metabolism and Digestive Diseases Grant R01-AM16845, "Transient Analysis of Counter Current Multipliers." |
| 1975-1977 | Principal Investigator, National Institute of General Medical Science Grant R01-GM21214, "Dynamics of Chemostat Cultures." |
| 1978-1980 | Principal Investigator, National Institute of Environmental Health Sciences Contract N01ES-2123, "Statistical Development of Carcinogenesis Models." |

### B. Committees and Offices

| | |
|---|---|
| 1978-1979 | United States Congress Office of Technology Assessment; member of Tolerance Advisory Panel-Environmental Contaminants in Food. |
| 1979-1980 | National Academy of Sciences; member of Diesel Impacts Study Committee and Panel on the Health Effects of Diesel Emissions. |
| 1976-1979 | Officer, Louisiana Chapter American Statistical Association<br>Secretary-Treasurer 1976-1977<br>Vice-President 1977-1978<br>President 1978-1979 |
| 1980-1983 | American Statistical Association; member of Committee on Statistics and the Environment |
| 1981-1982 | National Academy of Sciences; member of Committee on Institutional Means for the Assessment of Risks to Public Health |

### C. Selected Miscellaneous Activities

| | |
|---|---|
| 1972 | National Heart and Lung Institute; (consultant) Investigated transient behavior of solute cycling concentrating machines. |
| 1972 | National Institute of Environmental Health Sciences; (consultant) analyzed mathematical models for estimating the mutation rate in cell populations. |
| 1976-1977 | National Institute of Environmental Health Sciences; (consultant) developed statistical methodology for use with animal cancer experiments. |

C. Selected Miscellaneous Activities (continued)

| | |
|---|---|
| 1977-1978 | United States Congress Office of Technology Assessment; prepared background paper on risks to humans from drugs and chemicals in livestock feeding. |

## Publications in Refereed Journals

1. Crump, K. S. and Mode, C. J. (1968). A general age-dependent branching process I. Journal of Mathematical Analysis and Applications 24, 494-508.

2. Crump, K. S. and Mode, C. J. (1969). A general age-dependent branching process II. Journal of Mathematical Analysis and Application 25, No. 1, 8-17.

3. Crump, K. S. and Mode, C. J. (1969). A branching process with correlations among siblings. Journal of Applied Probability 6, 205-210.

4. Crump, K. S. (1970). On systems of renewal equations. Journal of Mathematical Analysis and Applications 30, No. 2., 425-434.

5. Crump, K. S. (1970). On systems at renewal equations: The reducible case. Journal of Mathematical Analysis and Applications 30, No. 3, 517-528.

6. Crump, K. S. (1970). Migratory populations in branching processes. Journal of Applied Probability 7, 565-572.

7. Crump, K. S. and Hoel, D. G. (1970). Some applications for renewal theory on the whole line. Journal of Applied Probability 7, 734-746.

8. Crump, K. S. and Howe, R. B. (1972). Nonparametric estimation of the age of a Galton-Watson branching process. Biometrika 59, 533-538.

9. Hoel, D. G. and Crump, K. S. (1974). Estimating the generation-time of an age-dependent branching process. Biometrics 30, 125-235.

10. Crump, K. S. and Hoel, D. G. (1974). Mathematical models for estimating mutation rates in cell populations. Biometrika 61, 237-252.

11. Crump, K. S. and Howe, R. B. (1974). Estimation of the age of a Bellman-Harris branching process. Mathematical Biosciences 19, 175-184.

12. Crump, K. S. (1975). On point processes having an order statistic structure. Sankhya 37, Series A, 396-404.

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26. Crump, K. S. (1978). Low-dose extrapolations of animal carcinogenicity data (reply to the letter of Nathan Mantel). Cancer Research 38, (June issue).

27. Crump, K. S. (1978). Models for carcinogenic risk assessment (Technical Comment), Science 202, 1106.

28. Crump, K. S. (1979). Dose response problems in carcinogenesis. Biometrics 35, 157-168.

29. Daffer, P. Z., Crump, K. S., and Masterman. M. D. (1980). Asymptotic theory for analyzing dose response survival data with application to the low-dose extrapolation problem. Mathematical Biosciences 50, 207-230.

30. Crump, K. S. (1981). An improved procedure for low-dose carcinogenic risk assessment from animal data. Journal of Environmental Pathology and Toxocology, Vol. 5, No. 2, 675-684.

31. Crump, K. S. (1982). Designs for discriminating between binary dose response models with applications to animal carcinogenicity experiments. Communications in Statistics, 11(4), 375-393.

32. Crump, K. S. and Sims, S. E. (1982). The quantitative effect of migration upon geographic studies. American Journal of Epidemiology (submitted).

33. Krewski, D., Crump, K. S., Gaylor, D. W., Portier, C., Salsburg, D., Sielken, R. L., and Van Ryzin, J. (1982). A comparison of statistical methods for low-dose extrapolation utilizing time-to-tumour data. (to appear).

## Other Publications, Reports, Etc.

1. Johnson, A. M. and Crump, K. S. (1976). Transient solution of a solute cycling model of the renal medulla using Laplace transforms. Proceedings of the 1976 Summer Simulation Conference, 460-463.

2. Guess, H. A. and Crump, K. S. (1977). Best-estimate low-dose extrapolation of carcinogenicity data. Environmental Health Perspectives 22, 149-152.

3. Guess, H. A. and Crump, K. S. (1977). Can we use animal experiments to estimate 'safe' doses for chemical carcinogens? Environmental Health: Quantitative Methods: 13-30. SIAM, Philadelphia (ed. by Alice Whittmore).

Other Publications, Reports, Etc. (cont.)

4. Langley, C. H. and Crump, K. S. (1977). Possible advantages and disadvantages of nontransmitted single-cell human mutagenesis assays. Zentrallaboratarium fur Mutagenitatsprufung (Conference on population monitoring methods for detecting increased mutation rates, 1976), 83-85.

5. Crump, K. S. (1978). Estimates of Risks to Humans from Chemical Residues in Meat. Prepared for the United States Congress Office of Technology Assessment.

6. Crump, K. S. (1978). Estimation of Mean Pesticide Concentrations When Observations are Detected Below the Quantification Limit. Prepared for Food and Drug Administration.

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Mr. GORE. Let me point out, in cases of 20,000 extra cases of cancer——

Dr. CRUMP. I have not done that arithmetic.

Mr. GORE. Based on 200 million people.

Dr. CRUMP. I will take Dr. Nelson's word for it.

Mr. GORE. Well, we will come back with questions, but, briefly, as I try to understand your testimony, Dr. Crump, what has been changed here is not only established principles of biology but also statistics.

Now, let us move back to biology. I want to add a special welcome to Dr. Richard Griesemer, a fellow Tennessean, the distinguished director of the Biology Division of Oak Ridge National Laboratory.

Dr. Griesemer, please proceed.

## STATEMENT OF DR. RICHARD GRIESEMER, DIRECTOR, BIOLOGY DIVISION, OAK RIDGE NATIONAL LABORATORY

Dr. GRIESEMER. Thank you, Mr. Chairman.

I am Richard Griesemer. I have doctoral degrees in veterinary medicine and in pathology and am a diplomate of the American College of Veterinary Pathologists. I am one of those pathologists that Mr. Walker referred to.

I was formerly a member of the staff of the National Cancer Institute, associate director of the Division of Cancer Cause and Prevention, and deputy director of the National Toxicology program. There I directed the Government's bioassay program for testing chemicals to see if they are capable of causing cancer.

I am very pleased, Mr. Chairman, to have an opportunity to comment on the EPA's risk assessment of formaldehyde, because I, too, with my colleagues on my left, believe that cancer risk decisions on chemicals as important as formaldehyde should have a scientific review as well as an opportunity for public input.

There have been four reviews of the possible carcinogenicity of formaldehyde, one by the Federal Panel on Formaldehyde which Mr. Gore referred to. This was a panel of 16 scientists from 8 Government agencies, including the Environmental Protection Agency, who reviewed the published and unpublished data available in 1980 and concluded that formaldehyde is an animal carcinogen and that, further, it would be prudent to regard formaldehyde as posing a carcinogenic risk to humans.

If there was any subsequent review by the American Cancer Society—and on that distinguished committee, among others, was Dr. Nelson, who is here at the table—they reached a similar conclusion.

In October last year, the International Agency for Research on Cancer reviewed formaldehyde and its carcinogenicity and reached the same conclusions. Then again last February, another committee of the International Agency for Research on Cancer weighed the evidence for the carcinogenicity of formaldehyde and other compounds, and this group as well concluded that there is sufficient evidence to establish that formaldehyde is carcinogenic for animals. Again, I think there is no question about that point.

I would like to turn my comments to some specific areas in the Todhunter memo which I think might serve as examples for the kinds of comments scientists and the community might have offered to EPA if they had had that chance.

First of all, in the memo the discussion on methods for evaluating chemical carcinogens from experimental data start with examples of usage. Scientists would normally start, I think, with definitions or with decision rules or criteria. The examples of usage that are given, for me, were misleading, because formaldehyde was not the example that was used. Rather, it suggested strongly that a compound has to be carcinogenic in at least two species and in both sexes for the evidence to be sufficient.

The sources cited from the IARC and a publication of mine are much more detailed and specific than that, and Dr. Nelson has already referred to the criteria for sufficient evidence for carcinogenicity and formaldehyde meets all of those, and I think it would have been relatively straightforward just to have said so in the memorandum.

For your information, formaldehyde does cause cancer of the nose in two strains of rats at dose levels of around 14 or 15 parts per million. There is supporting evidence for the induction of nasal tumors at lower dose levels in the rat and in the mouse as well. There is evidence for mutigenicity and damage to the genetic apparatus of cells. There is supporting evidence from other short-term tests including in vitro cell transformation assays. So there is a body of experimental data, all of which point in the same direction.

In his memo Dr. Todhunter goes on to say that the significance of the production of nasal tumors in rats is weakened by the results of other animal studies.

On pages 6 and 7 of the memorandum he refers to the bioassays in such a way as to state that, "There appears to be a high degree of species specificity and a strong dependence on the route of exposure." Neither of these statements is supported by the facts.

So far as species specificity is concerned, there is only one other study in the mouse, that one by CIIT, the same group that performed the bioassay in the rat, and that study was limited because there was considerable fighting among male mice, early mortality, and other competing causes of death, which reduced the numbers that were available for analysis—they that might have been at risk to cancer developing late in the life of the mouse.

Even so, the statistical analysis in the final report shows that when adjustments are made for early deaths, the value, Dr. Crump, is .0574, and the level of significance is .050. I submit those are essentially the same numbers. In hamsters, the only other species studied, the experiments were not designed to test for carcinogenicity of formaldehyde. I was a coinvestigator on some of those studies, so I can speak from experience. The hamsters' noses were not systematically examined in the way that the rats were, and, moreover, hamsters do not live as long as rats. The median time of survival in the hamster is about 18 months. Few of them live beyond 20 or 22 months in the experiment cited, and that is scarcely long enough for many cancers to develop.

Mr. GORE. What you are saying is that, in your view, Dr. Todhunter simply misinterpreted the study that you conducted?

Dr. GRIESEMER. I think he at least did not consider fully the limiting factors in the several studies that he cited. The evidence is not that formaldehyde has a greater specificity for the rat but in fact that only the rat has been adequately tested.

Regarding routes of exposure, only two routes have been explored with formaldehyde itself—the inhalation route, which is positive, and the subcutaneous route of administration, which is also positive. So I do not see any evidence that there is any difference in routes of exposure, as most of the potential routes, including the oral route, have not been studied.

Another issue in the memo is locations in the body where cancers might be expected to occur. One of the possible confounding factors in making that evaluation is that in the rat studies so many of them died very early in life from nasal cancers—fatal cancers—that there were very few that might have been at risk to cancers in other parts of the body.

Moreover, in the CIIT study the tissues in the body, other than the nose, were not examined at the exposure levels out of 5.6 and 2 parts per million. Only the high dose and the control animals were fully examined. So we really do not have any data on the intervening intermittent dose levels.

Another possible confounding factor in such an analysis is that people breathe through their mouths as well as through their noses, and one might therefore expect that cancers in people might occur in the throat or the upper digestive tract as well as in the lung and lower portions of the respiratory system.

In the CIIT study there were lesions found in the lung. In addition, there were two cancers of the lachrimal gland, which tell us that other parts besides the nose may be affected by formaldehyde in experimental systems.

Another issue I would like to mention is the qualitative differences in response that are raised on page 8 of the memorandum. In the memorandum it is said that at low exposure levels or short exposure times the hyperplastic or metaplastic effects of formaldehyde were reversible. There are two further statements that could easily have been made. One is that hyperplasia, by definition, is reversible. Hyperplasia is an increase in numbers of normal cells. When the stimulus is removed, we expect it to be reversed.

For the metaplasias, it might have been recognized that there are two kinds of metaplasias in such experiments. There is one that occurs early after exposure to chemical carcinogens which is reversible and in a late-appearing metaplasia which may or may not be reversible.

There are quantitative dose-related differences in these studies, but I do not know of any basis for proposing qualitative differences from the data available.

In the CIIT study itself, reversibility was examined to some extent, as reported in the memo, but the numbers of animals were very, very small and I do not think definitive conclusions can be drawn.

For example, at 27 months of the experiment, 3 months after the exposure had stopped, there were only nine female mice and five male rats examined, and the numbers are just too small.

The memo states that the cancers are always preceded by hyperplasia, metaplasia, and cytotoxicity. In parentheses it says, "Simply put, the animals developed open sores in their nasal tissue, after which tumors appeared." I think this statement requires a response.

The only description of ulceration in this study is described in the appendix A of the Todhunter memorandum, and there the authors describe the ulcerations as single thin cells covering areas normally covered by five or more cuboidal epithelial cells. Now this is not ulceration; this is not even erosion, but just simply that there were fewer cells per unit area and the ones that were left had to stretch out to cover the nasal lining.

In the CIIT final report I only found one mention of ulceration on page 138 where it is said that there are foci of ulceration or erosion in rats exposed to 14.3 parts per million formaldehyde for 6 months and sacrificed at that point. Throughout the CIIT report there are no references, other than that one, to ulceration. There are no open sores in the study, as said in the memo. The only possibility I can think of for open sores might be cancerous tissue protruding through the nostril or having invaded the bones and skin of the face protruding on the surface of the head of the animal.

The issue of cytotoxicity is one that is common to almost all chemical carcinogenesis study. Most chemical carcinogens are cytotoxic. We take advantage of that in cervical cancer in doing pap smears or looking at sputum cytologies in smokers, looking for plastic changes. So the fact that cytotoxicity occurs and is followed by metaplasias and displasias is to be expected in such studies. One can take advantage of it. From the viewpoint of mechanisms however, we cannot clear statement for formaldehyde or, to my knowledge, for any other chemical about whether the cytotoxicity is prerequisite for cancer formation or whether it is just an incidental associated finding.

So far as thresholds go, the only evidence I can find in any of the data is that formaldehyde does occur normally in the body at small amounts and for practical purposes that is a level below which we cannot reach. And so I suppose that makes it a threshold.

Obviously, any additional exposures can be considered to increase the risk of cancer.

One perhaps last example of issues in the memo that I think should be challenged is the absence of statements about benign tumors in the CIIT study. There were in fact so-called benign tumors in all exposure levels in the rat study, in the two-part per million level. They were described as papillary adenomas, and two malignant counterparts were found in higher doses, so that there appears to be a spectrum of benign to malignant tumors in all the dose levels in the rat study.

I believe that the data indicate that formaldehyde gas is carcinogenic in rats—exposure levels as low as two parts per million—for at least four reasons. One is that both carcinomas and adenomas are related to formaldehyde administration. Second, most tumors that are diagnosed as benign in carcigenicity studies are in fact only in a benign state at the time they are diagnosed, and histologic methods alone do not permit us to tell what the biologic potential of such tumors might be if they had been permitted to grow. Third, there appears to be a spectrum from benign to malignant tumors for this histologic type; and, fourth, there are no chemicals known that produce only benign tumors.

So, Dr. Crump, I think you will have to redo your statistics because, in my opinion, two parts per million is a carcinogenic dose level for rats.

I believe then that in the memorandum Dr. Todhunter has understated the case for the carcinogenicity of formaldehyde and the significance of these findings for humans. Virtually everyone is exposed. We are all exposed to some extent.

We also know that formaldehyde acts not only as a complete carcinogen but can act as a cancer initiator or as a cancer promoter, and therefore exposure to formaldehyde might add to the carcinogenicity of other chemical substances.

For mutagenicity there is direct evidence that that is the case—that enhanced mutagenesis is demonstrated when formaldehyde exposures are combined with exposures to hydrogen peroxide, to X-rays, and to ultraviolet light.

These then are some of the highlights of what I would have told the Environmental Protection Agency if I had been asked. Of the conclusions reached regarding the animal studies on pages 5 and 6 of the memorandum, I can only agree with two out of seven, and I believe the memorandum should be withdrawn and the subject reconsidered.

[The prepared statement of Dr. Griesemer follows:]

# TESTIMONY PRESENTED TO THE SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT of the COMMITTEE ON SCIENCE AND TECHNOLOGY

May 20, 1982
Washington, D.C.

Richard A. Griesemer
Director, Biology Division

OAK RIDGE NATIONAL LABORATORY*
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for the
DEPARTMENT OF ENERGY

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1. I, Richard A. Griesemer, D.V.M., Ph.D., am presently Director of the Biology Division of the Oak Ridge National Laboratory, Oak Ridge, Tennessee. I received the doctoral degree in veterinary medicine in 1953 from the Ohio State University and the Ph.D. degree in veterinary pathology in 1959 from the same institution. I am a diplomate of the specialty board, the American College of Veterinary Pathologists.

2. My scientific career has been dedicated primarily to research on diseases of the respiratory organs with particular emphasis on cancer. From 1977 to 1980 I was Associate Director of the Division of Cancer Cause and Prevention at the National Cancer Institute and concurrently Deputy Director of the National Toxicology Program where I directed the Federal Government's efforts to identify chemicals that cause cancer.

3. I am pleased to have the opportunity to comment on the scientific basis of the Environmental Protection Agency's carcinogenic risk assessment of formaldehyde. Whether of not the actions of the Environmental Protection Agency are justified, I believe that cancer risk decisions regarding substances with as much commercial and environmental importance as formaldehyde require scientific review and an opportunity for public input. I will concentrate my remarks on those portions of Dr. Todhunter's memorandum of February 10, 1982 (1) that deal with the experimental evidence for the carcinogenicity of formaldehyde and the significance of these findings for human risk assessment.

4. The possible carcinogenic effects from long-term exposure to formaldehyde have been reviewed by the Federal Panel on Formaldehyde (2), which I chaired. The Panel, convened under the auspices of the National Toxicology Program by the Consumer Product Safety Commission, was comprised of 16 scientists from eight federal agencies, including the Environmental Protection Agency. From its review of published and unpublished studies, the Panel concluded that

definitive experiments exist which demonstrate the mutagenicity and carcinogenicity of formaldehyde under laboratory conditions. Formaldehyde induced both gene mutations and chromosomal aberrations in a variety of test systems. By inhalation, formaldehyde caused cancer of the nose in rats. The concentrations of formaldehyde in inhaled air that caused nasal cancer in Fisher 344 rats are within the same order of magnitude as those to which humans may be exposed. The Panel further concluded that it is prudent to regard formaldehyde as posing a carcinogenic risk to humans.

5. The carcinogenicity of formaldehyde has also been reviewed by the International Agency for Research on Cancer (3). Using the criteria referred to by Dr. Todhunter on page 3 of his memorandum, an international committee of scientists concluded that there is sufficient evidence to establish the carcinogenicity of formaldehyde gas for animals and that the evidence from human studies is not adequate as yet for evaluation.

6. Dr. Todhunter, in his memorandum, begins his discussion of the methods for evaluating chemical carcinogens from experimental data by giving "examples of usage" rather than by giving definitions or decision rules. I found this approach misleading because the examples indicate that the compound has to be carcinogenic in at least two species and in both sexes for the evidence to be sufficient. In contrast, in both the International Agency for Research on Cancer report and the report by Griesemer and Cueto referred to by Dr. Todhunter, "sufficient evidence" for carcinogenicity from experimental animal studies is defined as indicating that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumor, or

age at onset. Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure (4). When applied to formaldehyde, the finding in a controlled experiment of a very high incidence of a rare tumor (nasal carcinomas in rats) in both sexes of one species is sufficient evidence to establish formaldehyde as a carcinogen for animals. Moreover, this finding was supported by the occurrence of small numbers of nasal cancers at a second dose level and in mice and by evidence of mutagenicity and genotoxicity in short-term tests. The results of the Chemical Industry Institute of Toxicology study have been further confirmed by investigators at New York University using a different strain of rat. There is no doubt that formaldehyde is carcinogenic for animals.

7. Dr. Todhunter implies further that the significance of the production of nasal tumors in rats is weakened by the results of other animal studies. On pages 6 and 7 of his memorandum he refers to other formaldehyde bioassays in such a way as to state that there appears to be a high degree of species specificity and a strong dependence on the route of exposure. Neither conclusion is supported by the facts. Mice have not been tested adequately for carcinogenicity. In the only study in mice by the Chemical Industry Institute of Toxicology (5), early mortality from fighting and other competing causes of death reduced the numbers of male mice that were at risk to developing cancers late in life. Even so, the statistical analysis of nasal carcinomas in male mice in the high dose group, when adjusted for early deaths, revealed a P-value of .0574, essentially the same as the level of significance of .050. Studies in hamsters thus far have not been designed to detect the carcinogenicity of formaldehyde but rather to fulfill other research objectives Accordingly, the noses of experimental hamsters have not been

systematically and thoroughly examined and the animals have not survived long enough and in large enough numbers for definitive conclusions to be reached. It should be mentioned that acetaldehyde, a substance with a chemical structure similar to formaldehyde, produces cancers of the nose and larynx in hamsters. The statement in the memorandum that the rat is unusually sensitive to the carcinogenic effects of formaldehyde is not supported by the data. Regarding routes of exposure, formaldehyde itself has only been tested adequately by the inhalation and subcutaneous routes and both are positive. From the available data, it is likely that no matter what the route of exposure formaldehyde would exert its greatest carcinogenic effect at the portal of entry where the doses delivered to the tissues would be the highest.

8. The locations in the body where cancers can be expected to occur are important for health risk assessment. Dr. Todhunter correctly notes that in general there is good concordance between the sites at which cancers occur in humans and in experimental animals after exposure to the same carcinogen. A possible confounding factor in the assessment of the bioassay of formaldehyde, however, is that so many rats died at a young age from fatal nasal cancers that there were relatively few at risk to late developing cancers at other sites. Another possible confounding factor is that people exposed to formaldehyde gas can be expected to breathe through their mouths (and in much larger quantities than mice or rats) so that in humans the mouth, throat, and lung also are potential target sites. In rats in the Chemical Industry Institute of Toxicology study, dysplastic and metaplastic lesions were found in the trachea, bronchi, and bronchioles and two carcinomas were found arising in the lacrimal ducts indicating that sites other than the nose are at risk in animals, too.

9. The question of qualitative differences in response at different dose levels is introduced on page 8 of his memorandum where Dr. Todhunter states that at low exposure levels or short exposure times the hyperplastic and metaplastic effects of formaldehyde were reversible. Two further statements could have been made. First, hyperplasias, which are increased numbers of normal cells, are all reversible when the stimulus is removed, no matter what the cause, dose level or exposure time. Second, there are two kinds of morphologically similar metaplasias that are typically found in this type of experiment and should be distinguished, an early reversible metaplasia and a late-appearing metaplasia that may or may not be reversible. Quantitative, dose-related differences are expected but there is no basis for proposing qualitative differences in response. In the Chemical Industry Institute of Toxicology experiment, where an attempt was made to examine the question of reversibility of metaplasia, no definitive conclusions can be reached because of the few animals in the test groups. (At 27 months, 3 months after cessation of exposure, 0 male mice, 9 female mice, 5 male rats, and 0 female rats from the high dose group were sacrificed. No mice or rats from the high dose groups were available for study at the 30 month sacrifice point). In my opinion, the statement that a higher exposure level or longer exposure time may produce a qualitatively different outcome has no scientific basis other than the possibility, based on data not presented by Dr. Todhunter, that there may be a different spectrum of histologic types of cancers produced at different dose regimens. The outcome, cancer, would still be the same, however.

10. The statement on page 8 of the memorandum, "In the CIIT bioassay, the development of nasal carcinomas was always preceded by hyperplasia, metaplasia and overt signs of cytotoxicity to the nasal mucosa (simply put, the animals

developed open sores in their nasal tissues after which tumors appeared)" requires comment. In the source cited (Appendix A of the memorandum), areas of ulceration were described as having single thin cells covering areas normally covered by five or more cuboidal epithelial cells. Such changes are more correctly called erosions rather than ulcerations. Moreover, the erosions were limited to the first 5 to 9 days of the study and to the 14.3 ppm dose level. The only possible "open sores" were exposed masses of cancer cells that protruded through the nostrils or had invaded and replaced the bones and skin of the face. The role of cytotoxicity in the disease process is unknown. Almost all chemical carcinogens are cytotoxic (kill cells) at high dose levels. For none of them, including formaldehyde, is it known whether the cytotoxicity is prerequisite for cancer formation or just an incidental associated finding. It should be emphasized, however, that in the CIIT study cytotoxicity was minimal at the 5.6 ppm dose level and not detected at the 2.0 ppm dose level, yet tumors formed in the noses of some rats at both dose levels. It is not known if formaldehyde is cytotoxic for humans at various dose levels. Having that information, however, would not help in assessing the risk of cancer to humans because the mechanism of cancer induction is unknown. The only evidence that there may be a threshold for carcinogenicity is that small amounts of formaldehyde are found normally in the body. The practical threshold therefore is the endogenous level of formaldehyde and any additional exposure from exogenous sources can be considered to increase the risk of cancer.

11. To provide the proper data base for dose extrapolation it is necessary to consider the so-called benign tumors as well as the malignant tumors that were produced in rats by inhalation of formaldehyde. In the Chemical Industry Institute of Toxicology study, tumors diagnosed as papillary adenomas were found in rats at all three concentrations of formaldehyde (2, 5.6, and 14.3 ppm)

in numbers that were statistically significantly increased over those in matched control rats as well as those in historic control rats of this strain. Two carcinomas that appeared to be malignant counterparts of the benign tumors were also found. I believe that these findings indicate that formaldehyde gas is carcinogenic for rats at exposure levels as low as 2 ppm for the following reasons. (a) The appearance of both carcinomas and adenomas is related to formaldehyde administration. (b) Most tumors diagnosed as benign in experimental animal studies are in fact only in a benign state at the time of diagnosis; histologic methods alone do not permit assessment of the biologic potential of such tumors if they had been permitted to grow. (c) A spectrum of benign to malignant tumors appears to exist for this histologic tumor type. (d) No chemicals are known that produce only benign tumors.

12. It is prudent to assume that dose levels of formaldehyde that are carcinogenic for rats by inhalation are also carcinogenic for humans, until human data to the contrary are obtained. In assessing the relevance of experimental data to the evaluation of carcinogenic risk to humans, the International Agency for Research on Cancer (6) states that, "In the present state of knowledge, it would be difficult to define a predictable relationship between the dose of a particular chemical required to produce cancer in test animals and the dose which would produce a similar incidence of cancer in humans. The available data suggest, however, that such a relationship may exist, at least for certain classes of carcinogenic chemicals. Data that provide sufficient evidence of carcinogenicity in test animals may therefore be used in an approximate quantitative evaluation of the human risk at some given exposure level, provided that the nature of the chemical concerned and the physiological, pharmacological and toxicological differences between the

test animals and humans are taken into account. However, no acceptable methods are currently available for quantifying the possible errors in such a procedure, whether it is used to generalize between species or to extrapolate from high to low doses."

13. I believe that in his memorandum, Dr. Todhunter has understated the case for the carcinogenicity of formaldehyde and the significance of this finding for humans. Formaldehyde gas is clearly carcinogenic for animals at exposure levels not greatly different from those to which people may be exposed. Because the concordance between human and animal carcinogens is essentially 100%, formaldehyde must be considered a carcinogen for humans too. My personal experience as a pathologist is that persons who work with formaldehyde and who are frequently exposed to irritating levels of formaldehyde gas develop a partial tolerance and continue to work in highly contaminated environments unaware of the health risks. Moreover, because formaldehyde may act as a cancer initiator, a cancer promoter, or as a complete carcinogen, the possibility that formaldehyde might add to the carcinogenicity of other chemical substances must also be considered.

14. I conclude that action by the Federal Government is necessary. Everyone is exposed to formaldehyde to some extent. Additional, unnecessary exposures must be avoided. I recommend that research be expanded to develop better methods to detect and measure formaldehyde in the home, the workplace, and the environment. While epidemiologic studies are in progress to better define the risks, efforts should be made to inform the public and to make interim recommendations, such as how to determine whether you need to change the ventilation in your home to protect your family.

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Dr. **GRIESEMER**. Thank you.

Mr. **GORE**. Thank you very much.

That last statistic you offered indicates that in your view this substance causes cancer in rats at exposure levels that are the same as the exposure that human beings experience routinely in a number of industries. Is that correct?

Dr. **GRIESEMER**. That is correct.

Mr. **GORE**. So it is not a question of having a massive dose of the substance causing cancer in an animal population and then extrapolating downward to lesser levels to see what the effect might be for human beings. You are talking about the same exact level of exposure.

Dr. **GRIESEMER**. Yes. As a pathologist I have been exposed to such levels—around two parts per million—6 days a week for 25 years.

Mr. **GORE**. Yes. And some 26 million Americans in various occupations are so exposed. If the risk levels that Dr. Crump cited are accurate, then you are talking about a very large number of extra cancers probably.

Let me begin my questions by trying to fix in my own mind exactly what has happened here.

The testimony you all have given is excellent, but it is really complicated, and it is hard for a layman to follow, whether it is biology or epidemiology or statistics; it is very, very difficult.

When you boil this issue down to its essence, it is not really the chemical interaction of formaldehyde with DNA or any of that stuff. What happened here is that an industry group 3 years ago wrote a letter to the Government and said, "Look, we have got test results indicating that formaldehyde causes cancer in animals"—an industry group. The Government said, "Well, we had better check it out." They established a panel of scientists and said:

> Look at this study that the industry did, and tell us whether or not you think there is an unreasonable danger to American citizens, particularly posed to all of those millions of Americans who are in daily contact with this substance.

The panel of scientists reported back a year later and said:

> We checked it out. We think the industry study is valid. It looks to us like it is definitely a carcinogen in animals, and you have to assume that it is a potential carcinogen in humans, and because we do not have any other way to protect the American people, we ought to proceed on a prudent basis to try to minimize the risk that Americans are probably facing.

Under the law, when that scientific panel reported back, a clock started ticking, and under the law a 180-day period started during which EPA had to decide what to do about it and whether to do anything about it. An election intervened, and a new team took over at EPA, and here come the lobbyists. The lobbyists for the Formaldehyde Institute, representing the folks who would lose some money, depending on what kind of protection was afforded the public against the substance they sell, went into the new team at EPA and said, "Hold your horses. Don't cost us some money. Don't take actions that are going to cut into our profits."

But the clock was ticking. So the new team at EPA said, "Let's take another look at the scientific evidence. Maybe we can stop the ticking of the clock. Maybe we can conclude that there is not really a risk, or there is not an unreasonable risk."

So at that point the scientific evidence was restudied, and Dr. John Todhunter, the new appointee at EPA, Assistant Administrator for Toxic Substances, on his own, did a new analysis of the scientific evidence and produced a memorandum telling the Administrator of EPA, "Don't worry. It looks to me like the science has been misinterpreted, and the way I review the scientific evidence, we should not do anything."

Now, you gentlemen, distinguished scientists in your field—and I could run through your credentials, but it would take too long—your peers know who you are—have looked at that second analysis of the scientific evidence and said, "What's this? This doesn't follow any accepted scientific principles. What is this stuff?" And, in dry, technical language, you have dissected the scientific analysis done by Mr. Todhunter. You have shown that it tracks almost exactly the biased view of the Formaldehyde Institute lobbyists. Perhaps that is coincidental; perhaps not. We will be inquiring into that later on. Of course he met with them to make sure he got their views. He did not meet with you; he did not meet with experts in the field outside of these folks.

Mr. SHAMASKY. Would the chairman yield a moment?

Mr. GORE. Yes.

Mr. SHAMANSKY. As you were reciting the events that happened, it occurred to me that I was remembering an article in the Atlantic Monthly of December 1981 the Education of David Stockman, in which apparently Mr. Stockman got numbers he did not like, and he reprogramed the computer.

Is this one of the hallmarks of this administration—that you reprogram the computer if you do not get the—I thought I would inquire, Mr. Chairman.

Mr. GORE. The gentleman is going even farther than I was prepared to.

Mr. SHAMANSKY. But the analogy was so strong. I do remember that article. I think I remember it correctly. There was something in the press about it.

Mr. GORE. I believe I do remember an article that fits that description.

But in essence the issue is larger than simply formaldehyde. The issue is, as my colleague states, whether or not scientific analyses can be jiggered, whether the truth can be submerged in order to fit the special interest views of people who stand to make a buck out of continuing the present exposures. It is really pretty crass, it seems to me, and I take it from cutting through the scientific jargon that it seems that way to you, too.

Dr. Nelson, would you agree with that?

Dr. NELSON. I think you have expressed it eloquently. I agree with every word you have said.

Mr. GORE. Dr. Nelson, you are an eminent scientist in this field. What do you make of a document like this Todhunter memo? Well, I do not know; maybe I am not asking the question the right way, but is it unreasonable for me to conclude and for others on the subcommittee to conclude—and we will have questions from the minority in a moment—is it unreasonable for some of us to conclude that the views of the industry involved were expressed in the Todhunter memo to the exclusion of sound scientific principles?

Dr. NELSON. I think I will read a statement that will go into the record.

Mr. GORE. All right.

Dr. NELSON. This excerpt responds substantively to your question. I read:

> I say the document is remarkable—referring to the Todhunter memorandum—in the sense that in each issue examined an extreme position is taken relating to the probable nonsignificance of the data on formaldehyde. It would perhaps be understandable for such an analysis to be prepared by industry or a manufacturing firm using formaldehyde. To be put forward as a dispassionate examination of evidence by a public agency responsible in this country for protecting the health of the public from such agents, this memorandum must be viewed as irresponsible.

Mr. GORE. That is a pretty strong statement. Translated, what you are saying is that if you saw this memorandum and were told that it had been paid for by the Formaldehyde Institute and written by somebody working for them, you would not have any trouble understanding it, but if you were told that it was prepared by someone who was charged with the legal responsibility for protecting American citizens and discharging responsibilities under the laws passed by Congress, you view it as irresponsible.

Dr. NELSON. I do view it as irresponsible. I do not draw the conclusion that you imply.

Mr. GORE. What do you mean by that? I did not mean to imply that it was paid for, if that is what you mean.

Dr. NELSON. No.

Mr. GORE. Let me hasten to correct that.

Dr. NELSON. Surely. I do not want to put words in the mouth of either of us.

Mr. GORE. And I do not believe that.

Dr. **Nelson**. I do view it as irresponsible. I would not be surprised to see this issued from an industry or manufacturing firm which has a profit interest to protect. Is that clear?

Mr. **Gore**. Yes, sir, it certainly is.

I have a number of other questions, but I want to yield to my colleague, Mr. Shamansky.

Mr. **Shamansky**. Mr. Chairman, I would like to comment that I do not know anything to add to what Dr. Nelson has said. The issues are clear; I am not going to belabor them. In fact, it is irresponsible, and it looks as if the science of Dr. Todhunter has been prostituted; for whatever reason, I do not know, but I think that irresponsible is accurate in the description.

Thank you.

Dr. **Nelson**. I do not want the wrong implication to be—I was not implying that you, sir, made such a conclusion or even implication. I was simply saying that such an implication might be construed by some as carrying that with it.

I have never met Dr. Todhunter. I would not recognize him if I met him on the street. His credentials, I understand, are excellent. He is a young man and, accordingly, I suppose, somewhat inexperienced. He has been put into a position in which—I may be going beyond what I should say, but I will say it, sir—he has been put in a position in which he is under an administration which has firmly determined policies which are antiregulatory. His youth we must forgive; time will take care of that.

I have sympathy for a young person with inexperience put in this situation.

Mr. **Shamansky**. Mr. Chairman and Dr. Nelson, you touched on something which I am afraid is a consistent problem with this administration. We are getting appointees of the administration or civil servants who have been here many years who are under great constraints with respect to budget, who come up and say the most implausible things.

When they are a career civil servant, I have no trouble with that. I understand the difficulty that they are under.

With respect to the political appointees—the basic political appointees of the administration—who come up and say improbable things, frankly I have very little patience with them. You ultimately have to make up your own mind as to what is reasonable and what is not reasonable.

I just have to put up with this, but I am under an obligation to challenge these statements when they come before me, and if I do not believe them I have to say that.

I would like to comment, Mr. Chairman, if I may, that Dr. Griesemer's credentials are excellent, since he has those degrees from Ohio State University—a very wise choice on your part, Doctor. [Laughter.]

Mr. **Gore**. From Ohio State and the National Lab in Tennessee—you are really in good shape, Dr. Griesemer. If you could do graduate work in Pennsylvania, maybe——

[Laughter.]

Mr. **Gore**. The Todhunter memorandum states that in the industry bioassay the development of nose cancers was "always preceded by hyperplasia, metaplasia, and overt signs of cytotoxicity. Simply put, the animals developed open sores in their nasal tissues, after which the tumors appeared."

Dr. Griesemer, do you agree that tumors appear to be secondary to cell injury?

Dr. GRIESEMER. Mr. Chairman, there is no evidence to support the idea that the mechanism of carcinogenicity is known—that is, that there is a progression through cell death through regeneration to cancer. Cytotoxicity may play a role in the process, but we do not know.

I do not find the argument compelling in any direction. The statement could be said about almost every chemical carcinogen, and it does not help us any in evaluating the risk.

There is no evidence at all of such serious injury that the repair process to that injury would account for the cancers. The ulcerative and inflammatory lesions were restricted to the first nine days of the experiment. They were quickly repaired, and they were not present through the whole course of this experiment.

Mr. GORE. So on this technical point, this is an eccentric, rare, extreme view that is rejected by the mainstream of science?

Dr. Albert, what is the significance of the results of the NYU studies on formaldehyde?

Dr. ALBERT. These studies have been undertaken not particularly with formaldehyde in mind, but as an offshoot of our studies that we had demonstrated the carcinogenicity of another agent, bischlormethylether. That agent breaks down into formaldehyde and hydrochloric acid, which itself is an irritant.

Our studies then went on to demonstrate the carcinogenicity of the combined exposure to formaldehyde and hydrochloric acid and then to formaldehyde itself, so that in effect we have developed data that, together with the CIIT data, make a convincing case about the carcigenicity of formaldehyde.

In addition to that, our studies have relevance to the role of irritation, because the combined exposure to formaldehyde and hydrochloric acid vapor does involve the additional exposure to an irritant—namely, hydrochloric acid. The addition of hydrochloric acid did not affect the cancer response at all, which suggests that the role of irritation is probably not a major one.

In addition to that, exposure to hydrochloric acid vapor at substantial concentrations, did not produce cancer.

Mr. GORE. Dr. Nelson, a lot has been said about the failure to see evidence of formaldehyde carcigenicity in human population studies. In other words, a lot has been made of the fact that we do not have epidemiological evidence that this substance, which a lot of people have been exposed to, has in fact already caused cancer in human beings. Why do we not have evidence of that kind, and should we put any weight on the fact that we do not have such evidence?

Dr. NELSON. In the first place, epidemiological studies are intrinsically quite insensitive. They are easily capable of picking up a rare type of tumor, and nasal cancer would certainly be one of these.

As you are aware, I am sure, there has been some discussion of case reports. These have not been—to me, at least—disclosed in terms of the background information, their authenticity, and so on, so I cannot comment on those.

But the point is that unless the tumor outcome is rare, epidemiological techniques are likely to be unable to detect even a substantial incidence of tumors. Angiocarcoma in liver produced by vinyl chloride is such a rare tumor, and it became evident and signaled the problem. Almost certainly vinyl chloride produces tumors elsewhere in the body and are probably larger in number than those produced—than the angiocarcoma. There is some evidence to suggest that there is lung cancer. If so, maybe they are buried in the very high normal background of lung cancer found in persons in this country.

So even when epidemiologic studies are mature and complete in this country, we may have no proof. We certainly do not have valid negative evidence when such epidemiologic studies are still in progress and are very mixed in power and informativeness.

Mr. **Gore**. In fact, subcommittee staff informs me that there are preliminary studies now uncovering nasal cancers in people that appear to be related to occupational——

Dr. **Nelson**. This I referred to, but I have not seen the background information which would permit me to comment in a sound fashion on those reported nasal cancers.

Mr. **Gore**. Cancer is not necessarily site specific, is it? In other words, if a substance is found to cause cancer in one particular part of an animal's anatomy, it does not mean—does it?—that the only threat to human beings is in that same part of the anatomy?

Dr. **Nelson**. That is correct, sir. In animals aromatic amines produce tumors, for example, in the liver but in man they produce tumors in the bladder.

Mr. **Gore**. Dr. Griesemer, do you believe that the finding of natural levels of formaldehyde in rats not exposed to exogenous, or outside of itself, formaldehyde should be interpreted to mean that low levels of the substance are not harmful?

Dr. **Griesemer**. No, I certainly do not. Just because something occurs naturally in the body does not mean that it is not harmful at higher levels or, for that matter, even at the same level.

We all spend a great deal of time trying to avoid exposure to excess cholesterol, and I think that is a good example of something that is found normally in the body that most of us would agree poses some risk at higher levels.

So I do not find it comforting that formaldehyde is found normally in the body. I think additional exposures that are preventable should be avoided.

Mr. **Gore**. Are you familiar with the Hecht studies—Mr. Walker?

Mr. **Walker**. Thank you, Mr. Chairman.

Dr. Nelson, would you say that the science suggests at this point that formaldehyde should be banned?

Dr. **Nelson**. I do not think the word "banned" is the correct word here.

Mr. **Walker**. That is the word I used though.

Dr. **Nelson**. I know, but I say that that is not the correct word to be used. Vinyl chloride was found to be a carcinogen. It was found in the laboratory to be a carcinogen before action was taken. A few cases were found, and panic ensued. Banning was suggested, not by serious people—forgive me—but banning was suggested. Major regulatory cutbacks were suggested. In 1974, the year of the panic, vinyl chloride production dropped by some 25 percent. It had been increasing by 5, 6, and 7 percent per year. The following year it increased by about 35 percent.

Vinyl chloride is being manufactured now under controls which were regarded as insupportable, crippling, and paralytic to the industry, but the vinyl chloride industry is flourishing, and indeed I am told that the same vinyl chloride which was being thrown into the factory space and outside stacks is paying a large part, perhaps all of the costs, of the control.

Mr. **Walker**. So your answer to my question is that it should not be banned?

Dr. **Nelson**. I think that it is generally not necessary to ban things.

Mr. **Walker**. OK, so the specific answer——

Dr. **Nelson**. "Control" is the word I would choose.

Mr. **Walker**. OK. But the specific answer to my question is, formaldehyde should not be banned?

Dr. **Nelson**. I will give you a reprint of the editorial I prepared for the Journal of the National Cancer Institute at their invitation in which I talk about building boxes about nasty materials. One can build boxes around formaldehyde, and one can reduce the leakage. I think it is a needless waste of both of our times, sir, to talk about banning. This requires serious engineering study.

Mr. **Walker**. I will come back to that, but I am looking for a specific answer to my question. The answer to my question is that formaldehyde should not be banned, based upon the scientific——

Dr. **Nelson**. I am not in a court of law, and I will not answer that question that particular way.

Mr. **Shamansky**. Would the gentleman yield?

As a lawyer, you are badgering the witness; that is what you are doing. You are badgering the witness, and in law that is a reason to object.

Mr. **Walker**. I am seeking a specific answer to a question.

Mr. **Shamansky**. But you are badgering the witness. He has told you not to use "banning," and you are trying to force him into a thing that he said should not be proper, and you keep going back to it.

Mr. **Walker**. I thank the gentleman for his very wise comment.

But the specific answer to my question is that you do not think that formaldehyde should be banned?

Dr. **Nelson**. Mr. Walker, I think a careful study of this issue will show that probably some uses should be banned—some uses, some selected uses. And for others, I think unquestionably means for control can be found which will permit the production and use of formaldehyde for appropriate purposes.

I just refuse to be cornered into this narrow, simplistic, and actually irrational——

Mr. **Walker**. No. I think you make light of a very serious matter here. We have banned some chemicals based upon the kinds of risks that you delineated in your statement that exist for formaldehyde. We banned saccharin not too long ago. I think we made a mistake.

Dr. NELSON. We did not ban saccharin, sir.

Mr. WALKER. We certainly regulated it to the point that we——

Dr. NELSON. If you wish to debate that issue, I will do it, because I am quite familiar with it. The recommended procedure with saccharin by Dr. Kennedy, then Commissioner of FDA, was to put it in the role of sort of an over the counter drug and let the individuals decide how to use it or sell it across the counter as a nonprescription drug. It was never proposed to be banned by FDA.

Mr. WALKER. Not by FDA, but there were people who proposed at the time that it be banned, so that there are people who rationally decided, based upon the evidence before them, that saccharin should be banned.

Dr. NELSON. The world is full, sir, of people who have not thought issues all the way through.

Mr. WALKER. So the question I am asking you is, based upon the signs that you have before you, would you say that formaldehyde should be banned? And I understand you to say no.

Dr. NELSON. I did not say quite no.

Mr. WALKER. Dr. Albert, would you say that formaldehyde should be banned?

Dr. ALBERT. This is in effect a regulatory judgment, and this involves weighing the risks and benefits. A judgment like that——

Mr. WALKER. I am asking you as a scientist, based upon the science that you have seen. We are assessing science here. Based upon the science that you have seen or the science that you know of, would you say formaldehyde should be banned?

Dr. ALBERT. I regard formaldehyde as a probable carcinogen that ought to be controlled. The nature of the controls I leave to others. I am in no position to make a judgment.

Mr. WALKER. OK. So the specific answer to my question is that no, you would not necessarily say that science supports the idea that it should be banned completely?

Dr. ALBERT. I think science has little to do with the regulatory issue except to provide the scientific basis upon which the regulatory considerations act.

Mr. GORE. Would the gentleman yield?

Mr. WALKER. I would be glad to yield.

Mr. GORE. I would simply like to note that the Chair would like to remain within the subcommittee's jurisdiction, and regulatory issues concerning the nature of the response after the 4(f) decision is reached would really fall outside of the committee's jurisdiction.

It is not surprising then that the witnesses we have called would not feel comfortable addressing regulatory issues. The Chair will certainly allow the gentleman to proceed.

Mr. WALKER. I thank the gentleman for his observations. I have framed my question in exactly the same way these hearings were framed—based upon the science—and I would submit to the chairman that that is exactly the point—that what we are dealing with here is a regulatory issue.

Dr. Griesemer, would you say that formaldehyde should be banned?

Dr. GRIESEMER. As a scientist, I would prefer to restrict my comments to my field of expertise, which is the animal experimental evidence for carcigenicity.

Mr. **Walker**. Based upon that science, would you say it should be banned?

Dr. **Griesemer**. Again, it is outside of my area of expertise.

Mr. **Walker**. Dr. Crump, based upon the statistics that you have seen in the field, would you say that formaldehyde should be banned?

Dr. **Crump**. I am concerned about a potential risk from formaldehyde. I think the proper regulatory approach would require a wider analysis than I have carried out at this time, and I am not prepared to say what the proper response should be.

Mr. **Walker**. OK. So I gather then that where we are is that nobody will come flat out and say that we ought to ban it based on anything that they know, and I got the general idea that we should then regulate it.

Dr. Nelson, based upon the science that you have seen and know, at what level should we regulate it?

Dr. **Nelson**. I am not prepared now to respond to that in an explicit way. There are different facets to it. There is one level of concern for the general public. There is another level of concern for specific consumer groups. There is another level of concern for occupational exposures. This is a matter which involves health issues; it is a matter which involves technology; it is a matter which involves engineering replacements; it gets the chemical industry involved; it is a question of trade offs having to be made; it is not a zero risk world that we are living in.

I would hope that this country would not fall into the silly and stupid situation of just reacting with unintelligent knee jerks to these issues.

I have participated, as perhaps you have also, in determination of control levels. I will be happy to do so again as long as I can find the intellect and the time to do so, but these require careful study.

I will also say, sir—let me make one more point, please—that long experience has taught me that there is a certain kind of response to be anticipated—that each time a chemical of utility and of profit is threatened, the proposed controls will be challenged. This will lead and should properly lead to some kind of an iterative process in which the balance is achieved. This is a sociopolitical process between what society needs and what they are willing to pay for.

I must say that I have some concern about the ineptitude with which these decisions are made in this country, but nevertheless it is working crudely but is working. It is a sociopolitical debate which has sometimes tediously gone on and on but one has to anticipate certain kinds of automatic responses: "It will kill the industry." All right. It has not killed very many industries. I think that debate should start.

Mr. **Walker**. EPA regulates for the general public, not all these specific groups you talked about. They have a general public. At what level does the present science tell us we ought to regulate——

Dr. **Nelson**. I think I have responded as constructively as I can, sir, to that.

Mr. **Walker**. No. What you said was that there are various groups that come in, and you talked about the occupational people and all of this. They are regulated by somebody else. At what level would science indicate—you are testifying here on the science—at what level would science indicate that we ought to regulate formaldehyde?

Dr. NELSON. I do not restrict my sense of responsibility for the use of science to the constituency related to EPA. I am interested in the worker, and I am interested in many others.

Mr. WALKER. EPA is what we have before us.

Dr. Albert, at what level should formaldehyde be regulated?

Dr. ALBERT. The general approach to this issue in the EPA, which was established in the administration before this last one—it goes back two administrations—was to, wherever possible, weigh risks and benefits in making regulatory decisions and to recognize that carcinogens are nonthreshold toxicants and that there is no specific level to be achieved in regulatory action, but rather the exposures ought to be reduced as far as possible in light of the costs and the social consequences.

So the approach to the control of carcinogens inevitably comes out to be a balance between various forces; the scientific evidence provides the impetus toward regulation, and the engineering, the economic, and social consequences interact to develop a regulatory level.

Mr. WALKER. That is all fine, except you all are appearing here as experts. We brought you in here as scientific experts. We have heard—and I am sorry I missed part of it—the administration kicked around, I understand, for manipulating science and all kinds of things.

Now, it seems to me that if we are going to make those kinds of accusations, we ought to know what the science is that is being manipulated, and that science should allow us to make some judgments.

What I am getting from the panel is no sense of judgment whatsoever. You are appearing as scientific witnesses, and you are telling us that science indicates that we ought to regulate formaldehyde. Now I want to know, as experts, what level we ought to be regulating it at. I want to know what it is that EPA should be doing in terms of these regulations. What I am getting is a lap around the track.

I am asking some specific questions of each of you as scientists. I want to know, based upon scientific data, what it is EPA should be regulating in terms of the general public.

Dr. NELSON. May I make a statement here, sir—a brief one. Although I thank Mr. Shamansky for his intervention on my behalf, I frankly do not feel harassed, and I do not mind this debate with Mr. Walker.

Let me simply say that if you wish to join me now in launching the appropriate review procedures to establish controls, I will be glad to work with you. It cannot be done in this room, and you know that quite as well as I do.

Mr. GORE. Would the gentleman yield?

Mr. WALKER. I would be glad to yield to the gentleman in a moment.

The appropriate review procedures are in place, and EPA has made a decision based upon what it regards as appropriate review procedures. It decided not to regulate. You do not agree with the way in which they conducted their review, because you say science was manipulated. What was manipulated? What is the decision line that they should have used? What kind of science should they have used for their procedures, and what is the regulatory guideline that you say they should have developed? That is my question.

Dr. **Nelson**. You missed part of the presentation, Mr. Walker, and I think that you will find it in the record.

Mr. **Walker**. I apologize for that.

Dr. **Nelson**. The statement has been made that the Todhunter memorandum, which is one of the bases—maybe not the sole one—which went to the administration for her decision process was inadequate; it was biased and incomplete.

Further, it was said that that statement was apparently not reviewed within the agency, certainly not reviewed in a public peer review mechanism.

How to correct that is very straightforward. Open up this process to public debate. See to it that there is peer review, and go through the normal channels, which in fact have been outlined here.

I think the point to be made, which has been said repeatedly here, was that that memorandum—if that is the sole basis for inaction by EPA—was an inadequate basis, inadequate not only technically but inadequate in its review.

Mr. **Walker**. I will say to you—and then I will be very glad to yield to the chairman—that, No. 1, this was not a final decision by any stretch of the imagination; it was a decision not to put it on the fast track. The fast track involves making an assessment that substantial risk is involved—substantial risk.

I am saying that substantial risk involves making an assessment of data; I am saying that also regulation would involve making some assessment of data; yet I can find nobody here who is willing to give me those kinds of figures—that kind of data—on which they suggest that this whole thing should have been put on the fastest possible track. That is what my concern is.

I would be glad to yield to the chairman.

Mr. **Gore**. Let me come at your question from a slightly different angle. I wonder if any of you would feel comfortable in quantifying what you believe scientists generally regard as an unreasonable risk in this field—getting back to your "10 to the minus" numbers.

Where would the cutoff be for a definition—a generally accepted definition—of "unreasonable risk" that would or ought to start the relevant agencies looking at what they ought to do about it, without getting into the specific control mechanisms? What level of risk to the general population—1 in 100,000? Would 1 extra case of cancer in 100,000 people be an unreasonable risk? Do you feel comfortable answering that, Dr. Nelson—cause for concern?

Dr. **Nelson**. I seem to be occupying too much of your time, sir, but I will be glad to respond to this, if you will permit me to do one thing.

Mr. **Gore**. Surely.

Dr. **Nelson**. May I take off my hat as a scientist?

Mr. **Gore**. Yes.

Dr. **Nelson**. You are the expert in the area.

You are in a position of responsibility having to do with public policy in this country. The decision as to when a risk is acceptable or not acceptable is a decision of those affected, the people. You represent the people. You are the expert in determining what is an acceptable risk for society. You represent society.

I also represent society. I will join you now not as a scientist but as a citizen, not of your constituency perhaps, but as a citizen, and I would say that I find something like 10 to the −4 as perhaps acceptable for occupational situations where there are not a multiplicity of such hazards.

I am not at all happy with 1 in 10,000 for the general population—by no means. It has got to be something less than that.

Now, that is not a scientific statement at all. That is a ctizen's statement of what this country maybe willing to bear in the way of costs for the benefits secured.

You tell me when to put my scientist hat back on, and I will put it back on.

Mr. GORE. OK. I appreciate that—1 in 10,000 cases, or 10 to the −5 would be 20,000 extra cases of cancer.

EPA regulatory actions have been clustered around the 10 to the −5 figure or 1 in 100,000 cases in the past. Dr. Todhunter's memo stated that 10 to the −4—1 in 10,000 cases—is not sufficient cause for concern in his memo. So it is difficult to deal with this quantification, but I think we can get at it.

Now you can put your expert hat back on, unless Mr. Walker wants you to keep it off.

Mr. WALKER. No, Mr. Chairman. My real question then would be, what scientific data are there to indicate that we can generally accept statistics that show that for human beings formaldehyde represents a 1 in 10,000 potentiality. Are there any?

Dr. NELSON. There are at least two, perhaps three, people at this table that are more expert at this than I am.

Mr. WALKER. All right. I am basically asking the panel whether or not there is any—is there any scientific data to indicate that, to the general population, formaldehyde represents a 1 in 10,000 chance of cancer risk?

Dr. ALBERT. It is my understanding that there are circumstances in which the exposures can get up to several parts per million—for example in some mobile homes and in some homes that have been insulated with formaldehyde foam. Certainly these levels of exposure would be expected to be at least that risk or higher.

Mr. GORE. I think Dr. Crump wanted to respond also.

Dr. CRUMP. I described earlier some procedures that have been used by EPA previously which have been associated with determining ranges of risk in these situations.

When I applied the method described in the Todhunter memo to the median exposure of 0.01 ppm, which is also in this memo, I came up with a risk of 10 to the −4 for the general population.

Mr. WALKER. Based upon what scientific data?

Dr. CRUMP. The CIIT study.

Mr. WALKER. The CIIT study. What about the study being undertaken by DuPont of workers exposed to low levels of formaldehyde? Do you know the results of that one?

Dr. CRUMP. I have not seen the results of that study.

Mr. WALKER. They have a study out which shows that in none of their analysis—fairly extensive analysis— were formaldehyde workers' relative risk of cancer significantly greater than 1.0.

Dr. CRUMP. I am not at all surprised at that result. That result is probably also consistent with a risk that is considerably greater than 1 in 10,000, because, as Dr. Nelson has pointed out, these types of studies are very insensitive for detecting increases of that order.

Mr. WALKER. In their abstract, what they indicate is:

> In short, a thorough analysis of the data suggested that cancer mortality rates in the company's formaldehyde exposed workers were no higher than the rates among nonexposed coworkers.

Mr. GORE. If the gentleman would yield—is this a published study?

Mr. WALKER. It has just been released.

Mr. GORE. Has it been published?

Mr. WALKER. It was released on May 18, 1982 and as far as I know it has been released, yes.

Mr. GORE. There is a difference between released and published.

Mr. WALKER. It has not appeared in scientific literature.

Mr. GORE. Without objection, we will put it in the record. (See appendix 2.)

If the gentleman would yield further, let me also put into the record the revisions to the technical document at EPA on which Dr. Todhunter's memorandum was supposedly based. These revisions made sense of his memorandum. (See appendix 3.)

The EPA's own figures show that in one category of employment the estimate of risk is 5.6 times 10 to the −3. That is 5½ extra cases of cancer in 1,000 people. How would you define a level of risk of that kind, Dr. Nelson—extraordinarily high?

Dr. NELSON. Very high and totally unacceptable even in occupational situations in a country at peace.

Mr. GORE. In two other—you really give balanced answers; I like your testimony. In two other occupations, there are 1.93 times 10 to the −4. That is 2 extra cases in 10,000. In another occupation it is 3.6 times 10 to the −4. That is 3.5 extra cases in every 10,000 cases. Those are also pretty high levels. Would you say those were unreasonably high levels also?

Dr. NELSON. I do.

Mr. GORE. All right.

Mr. SHAMANSKY. Would the chairman yield?

Mr. GORE. I think the time still belongs to Mr. Walker, but we are interpreting the rule liberally.

Mr. WALKER. Yes. As I said, I am probably way over time, Mr. Chairman. I thank you for your indulgence.

Dr. Crump, how confident are you that risk assessments from animal data are accurate to predict human risk?

Dr. CRUMP. I think there is a great deal of uncertainty in estimates of human risk from animal data.

Mr. WALKER. Is it generally agreed within the risk assessment community that quantitative risk assessments are reliable predicters of human risk?

Dr. CRUMP. These methods have been developed to assist regulators in making decisions, and I believe that they are the best tools that we currently have available for assessing what the risks are, even though there are uncertainties involved.

Mr. WALKER. So in this case the uncertainties would have to weigh fairly heavily, would they not, since we do not have any real human data at this point to back up the animal data? Is that not a fair assessment?

Dr. CRUMP. I am not sure what you mean by the "uncertainties of"——

Mr. WALKER. You used the word "uncertainties," and for somebody who is having to develop regulations, what I am saying is, would not the uncertainties have to weigh rather heavily on their minds, since they do not have any human data to back up the animal data?

Dr. CRUMP. I think uncertainties can go in both directions. Even without the risk assessment, it is of concern, I think, that we have people who are exposed at levels very near those where we see positive results in animals.

Mr. WALKER. We have human beings that are being exposed to 15 parts per million?

Dr. CRUMP. Dr. Griesemer indicated he was exposed quite frequently to 2 parts per million, which is not very far, in my mind, from 15 parts per million.

Mr. WALKER. In the general population we have people who are exposed to 15 parts per million on any kind of regular basis at all?

Dr. CRUMP. I did not say people were exposed to 15 parts per million; I was citing Dr. Griesemer. He said he was exposed frequently to 2 parts per million.

Mr. WALKER. But that would be occupational and not under the jurisdiction of EPA.

Dr. CRUMP. He is a member of the general population.

Mr. WALKER. Yes, but he was saying in his profession, which is not the study of EPA regulation.

This chemical has been in general use for nearly 100 years. Do you know of any data that indicate a higher cancer rate for human beings over that 100-year period?

Dr. CRUMP. I honestly have not studied the epidemiological data carefully, but the answer to your question is no.

Mr. WALKER. Thank you, Mr. Chairman.

Mr. GORE. Have any epidemiological studies been done to attempt to find such evidence?

Dr. GRIESEMER. There have been a number of human studies of people exposed to formaldehyde that have been reviewed by both the Federal Panel on Formaldehyde and the International Agency for Research on Cancer.

The Federal Panel concluded that none of the studies that had been conducted up to that time were adequate for interpretation and recommended that some studies be conducted, and in fact there are a great many now in progress.

Mr. GORE. So there have been no adequate studies to arrive at that?

Dr. GRIESEMER. The International Agency found three studies, all of which had some evidence for carcinogenicity, one for skin, one for prostate, and one for the gastrointestinal tract, but they too concluded that the studies were limited and that further studies were needed.

Mr. GORE. Thank you very much.

Mr. Shamansky?

Mr. SHAMANSKY. Thank you, Mr. Chairman.

Dr. Albert, do you agree with the statement by Dr. Todhunter that nearly all individual risks from formaldehyde exposure fall into the range of 1 to 10 to the −6 to 1 times 10 to the −4 and that this is a range in which priority action is often not considered?

Dr. ALBERT. I have not participated in any quantitative analysis of formaldehyde risks which seriously depend on the validity of the exposure estimates, and these really require intensive expert efforts in order to develop them.

So I cannot comment. I certainly heard Dr. Crump, who indicated that he did not get the same answers that were in Dr. Todhunter's memo in terms of risk numbers.

As to the second question of whether or not priority action is not taken with risks that range from 10 to the −4 and below, I think there has been—it is my impression that there has been exceedingly little experience in the EPA in making decisions about what to list and what not to list on the basis of risk levels.

So it seems to me that no pattern has really been set, which is my perception of the matter.

Mr. SHAMANSKY. Based on your experience, do you believe that the EPA is changing whatever standards it had with respect to finding dangers in invoking controls?

Dr. ALBERT. I think what is going on now reflects a trend which began in the latter part of the last administration—namely, an antiregulatory trend—which has accelerated substantially in this administration, and I think a much harder look is being taken at the meaning of carcinogenesis evidence in relationship to the magnitude of human risk.

So my answer to that is that I do feel that there is much more resistance within the EPA to regulatory action now than there has been in the past.

Mr. WALKER. Would the gentleman yield?

Mr. SHAMANSKY. Certainly.

Mr. WALKER. Is that antiregulatory trend bad or good?

Dr. ALBERT. I am not making any judgments on that. That is, I think, your ballpark.

Mr. SHAMANSKY. Animal studies were used in regulating vinyl chloride. Do you think that it is appropriate to use animal studies with respect to formaldehyde?

Dr. ALBERT. Yes, I do. I think that the pattern that had been set 6 years ago in the EPA was to use animals as surrogates for human response.

I guess the strongest argument for it is that, when one looks at those agents which are known to produce cancer in humans, virtually every one of them produces cancer in animals, and the pattern of cancer response—the nature of the pathologic processes—is very similar in animals and humans.

Mr. SHAMANSKY. It would be good science then, as far as you are concerned——

Dr. ALBERT. Yes, I think it is generally accepted in the scientific community to use bioassay animals as surrogates for human cancer responses.

Mr. SHAMANSKY. Then it would be reasonable, in your opinion, for me as a legislator to use those studies to conclude that at a certain point formaldehyde could cause cancer in humans?

Dr. ALBERT. I believe so.

Mr. SHAMANSKY. Then I have a further obligation to determine how many people I choose to sacrifice before setting that limit—what is unreasonable in the workplace, it was pointed out, would be one figure for the general population and another figure—that is not an unreasonable distinction? It is one that Dr. Nelson made.

Dr. ALBERT. I think that the way you put it in terms of sacrificing people, I think, is stated to make a point, but I really think, in the interests of a balanced view of the matter, one has to keep in mind the uncertainties that are associated with these risk estimates.

The EPA has used quantitative risk assessment for the last 6 years, and I certainly have strongly advocated it, because I believe that some idea of the magnitude of the risk is essential to making judgments in the public health area.

But the way in which the EPA has put the quantitative risk assessments was always to emphasize that they are crude ballpark estimates. They provide what might be regarded as a plausible upper limit estimate. Things could be as bad as these estimates point out, but they could also be less.

So that when you are talking about sacrificing people, I think that is putting it a little strongly. We are not so sure that we are dealing with dead bodies lying on the ground. We are dealing with estimates that have a certain amount of plausibility, a certain amount of uncertainty, and I think that the issue is the extent of prudence which is to be exercised in dealing with these matters.

Mr. SHAMANSKY. I appreciate your commenting on my use of the word "sacrifice." It is a perjorative in that context; I concede that; I appreciate your pointing it out. But in dealing with these kinds of matters I have to exercise a judgment based on the figures to say that the probabilities are *x* number of people, given the population as a whole, will have cancer if this exposure is maintained, and mathematically there will be fewer people exposed if it is reduced. I have to exercise a value judgment.

Dr. ALBERT. Yes I think these estimates need to be taken seriously.

Mr. SHAMANSKY. Even though these may be crude figures, that does not mean they are invalid figures.

Dr. ALBERT. No.

Mr. SHAMANSKY. And I do think that there is such a thing as cost effectiveness. I would not go chase after the last one, but at some point or other it becomes reasonable as a matter of judgment, whatever value system a legislator has, to say, "I think this is unacceptable, given the cost," and so on and so forth. Is that the way you thought the EPA used to be run?

Dr. ALBERT. I think it still is in most respects.

Mr. SHAMANSKY. That is reassuring.

Thank you, Mr. Chairman.

Mr. **Gore**. Thank you, and let me express the thanks of the subcommittee to all of you for a very long period of questioning; we appreciate it; thank you very much.

Our next witness is Dr. Peter Preuss, Associate Executive Director for Health Sciences with the U.S. Consumer Product Safety Commission.

Dr. Preuss, would you come forward, please?

Dr. Preuss, we neglected, in conformity with the subcommittee's traditions, to swear in the first witnesses; it was an error. Would you stand and be sworn, please?

Are your colleagues going to be providing testimony also?

Dr. **Preuss**. Yes, sir.

Mr. **Gore**. Would you raise your right hands? Do you swear that the testimony you are about to give will be the truth, the whole truth, and nothing but the truth, so help you God?

Dr. **Preuss**. I do.

Dr. **Ulsamer**. I do.

Dr. **Cohn**. I do.

Mr. **Gore**. Thank you very much.

Could you identify your colleagues for the reporter?

## STATEMENT OF DR. PETER W. PREUSS, ASSOCIATE EXECUTIVE DIRECTOR FOR HEALTH SCIENCES, U.S. CONSUMER PRODUCT SAFETY COMMISSION, ACCOMPANIED BY DR. ANDREW ULSAMER AND DR. MURRAY COHN

Dr. **Preuss**. To my right is Dr. Andrew Ulsamer, and to my left is Dr. Murray Cohn, both of the Consumer Product Safety Commission.

Mr. **Gore** Dr. Preuss, your statement will be placed in the record, wjthout objection. Would you please proceed?

Dr. **Preuss**. Thank you very much, Mr. Chairman.

I would like to summarize my statement for you, if I may. My name is Peter Preuss. I am the Associate Executive Director for Health Sciences at the Consumer Product Safety Commission.

As you may know, on February 22, 1982, the Consumer Product Safety Commission voted to ban urea formaldehyde foam insulation, or UFFI. The Commission took this step because of its concern about the health effects associated with formaldehyde and its belief that the emission of formaldehyde from the foam could not be adequately controlled.

The Commission was petitioned in 1976 to control the potential hazards associated with a variety of insulations. During subsequent years the Commission received over 2,000 complaints from people who had installed UFFI in their homes and experienced acute health symptoms, such as irritation of the upper respiratory tract or of the eyes.

As a part of the effort to understand these acute effects, the Commission asked the National Academy of Sciences to review all the available information on the acute effects of formaldehyde and to make recommendations regarding the existence of a tolerable level of formaldehyde for indoor air.

The Academy concluded that there was no population threshhold for the irritant effects of formaldehyde. In addition, the Commission arranged to contract with the Franklin Research Institute to investigate the emission of formaldehyde from panels specially constructed to simulate the walls of homes which had been insulated with UFFI by the major suppliers of the insulation.

Finally, we held a series of public meetings around the country to obtain additional information from industry, academia, and the public.

It was during the course of these investigations and hearings that the Formaldehyde Institute notified us in October, 1979, of the early results of the Chemical Industry Institute of Toxicology [CIIT] bioassay experiments on the effects of formaldehyde exposure. At that time, the Formaldehyde Institute informed us that three of the rats exposed to 15 parts per million of formaldehyde for 6 hours per day 5 days per week for about 1 year had been found to have nasal cancer. This raised a concern about a possible cancer risk to large segments of the population, because many people in this country were known to be exposed to formaldehyde.

Since that time there has been a great deal of discussion and analysis—and, I might add parenthetically, a great deal of controversy—regarding the carcinogenicity of formaldehyde.

To resolve some of the issues, the Commission asked for and received a report from the Federal Panel on Formaldehyde, which was formed under the auspices of the national toxicology program.

In addition, the carcinogenicity of formaldehyde has been reviewed by a working group of the International Agency for Research on Cancer and by an independent panel at the Mount Sinai Medical Center in New York, who submitted a report to the American Cancer Society.

The National Institute for Occupational Safety and Health has also published a current intelligence bulletin on the subject of occupational exposure to formaldehyde.

All of these reviews came to the conclusion that formaldehyde was a carcinogen in animals and that it should be presumed to pose a risk of cancer to humans, or that human exposure to formaldehyde should be reduced or eliminated.

In your letter of invitation to me, Mr. Chairman, you asked that I evaluate the toxicological data from animal studies on formaldehyde related to carcinogenicity, the application of those animal data to the human situation, as well as the methods, processes, and assumptions that are a part of the quantitative assessment of potential human risk.

Let me begin with the reasons generally why I am concerned about the potential chronic effects of formaldehyde. My concern is based on metabolism, mutagenicity, and carcinogenicity studies. In brief, the biochemical studies show that formaldehyde reacts readily with other chemicals; including proteins and nucleic acids. It may also be converted to formate and excreted in urine or to carbon dioxide and exhaled. These reactions are similar in laboratory animals and man, although the reaction rates may vary.

Based on our present knowledge of formaldehyde biochemistry, free formaldehyde does not seem to exist in the body.

Formaldehyde is also mutagenic in bacteria, viruses, fungi, insects, and mouse lymphoma cells with or without metabolic activation. It induces chromosomal recombination in yeast, insects, and cultured mammalian cells, as well as cellular transformation in mouse cells. These results all indicate that formaldehyde is capable of binding to and altering genetic material.

Early studies on the carcinogenic potential of formaldehyde via inhalation exposure were negative but suffered from inadequate exposure or too few animals or incomplete pathological examinations. The recent study by the CIIT involved rats and mice exposed to 0, 2, 6, and 15 parts per million of formaldehyde for 6 hours a day, 5 days a week, for up to 24 months.

After 18 months of exposure, a total of 37 rats exposed to 15 parts per million of formaldehyde had developed nasal, squamous cell carcinoma.

Other changes observed during this study were the development in rats of squamous metaplasia, dysplasia, and polypoid adenomas. The number of rats with squamous cell carcinoma increased to 103 in the 15 parts per million exposure group after 24 months of exposure. In addition, 2 rats exposed to 6 parts per million and 2 mice exposed to 15 parts per million also developed squamous cell carcinomas of the nasal cavity.

A new study at New York University is currently being completed in which rats were exposed to 14 parts per million of formaldehyde with and without the addition of 10 parts per million of HCL as well as to 10 parts per million of HCL vapor alone.

Squamous cell carcinoma of the nasal cavity has developed in all exposure groups containing formaldehyde, while no nasal carcinomas have been observed in the HCL and control groups. These results further support the conclusions regarding the carcinogenic potential of formaldehyde.

At the present time, the available epidemiological studies of humans exposed to formaldehyde vapor are inadequate to assess its carcinogenic potential. In one of these studies, Wong identified some 2,000 chemical workers potentially exposed to formaldehyde and described the cause of death of the 146 workers who died. Marsh identified approximately 2,500 chemical workers and analyzed the causes of death of the 115 workers who had died. Walrath and Fraumeni of the National Cancer Institute studied some 1,100 embalmers who had died.

In these studies excess nasal cancer was not detected. However, a preliminary report on the cohort study by the National Cancer Institute has noted a significant increase in skin cancers as well as an increase in cancer of the brain. It is not clear at this time whether or not these cancers are associated with exposure to formaldehyde.

There are, in addition, two studies involving pathologists that have produced conflicting results. The first, a cohort of some 2,000 pathologists, of whom 181 had died, revealed no increase in cancer. The same was true for 154 pathology technicians who had died. A second study compared pathologists to radiologists and found increased cancer of the lung and lymphatic system in the pathologists.

These studies, however, all suffer from problems which prevent them from coming to any definitive conclusions regarding the carcinogenic potential of formaldehyde in humans. These shortcomings include the fact that the studies were not large enough and therefore statistically powerful enough to be sure of the ability to detect a significant carcinogenic response. Second, the duration and amount of exposure is not known. Third, cohorts were not always followed long enough to allow cancer to develop. Fourth, it is not clear if all workers of these cohorts were known to actually have been exposed to formaldehyde.

A new attempt to evaluate the potential human carcinogenicity of formaldehyde vapor has now been started by the National Cancer Institute and will include some 17,000 workers thought to have been exposed to formaldehyde. It is hoped that the results will be available in 2 to 3 years.

The second critical facet in the assessment of human risk is the determination of exposure to the chemical, as, clearly, the degree of risk is related both to the extent and the duration of exposure to the chemical in question.

Once exposure is established and a determination has been made that formaldehyde has the potential to pose a carcinogenic risk to humans, the process of risk assessment can be invoked. The risk assessment calculated by CPSC included a number of assumptions dealing with extrapolations between animal species and from high to low doses, the proportion of lifetime that the animals were exposed versus the proportion of lifetime that people might be exposed, as well as ideas about the way in which formaldehyde exposure might give rise to tumors.

One aspect of the risk assessment that deserves special mention, however, is our use of a methodology that includes a linear component at low doses. We have used such a methodology in addition to a "best fit of data" methodology because of the former's greater biological plausibility.

In the CPSC formaldehyde risk assessment there is a discussion of why the interaction of formaldehyde with other environmental carcinogens and background processes is more likely than the premise of formaldehyde acting independently. The reasons include the fact that formaldehyde, like many other carcinogens, can cause genetic damage by mutation.

Several studies have shown that formaldehyde can enhance the effect of other mutagenic agents, indicating that an interaction is occurring. There is also a study in animals in which formaldehyde was shown to increase the number of tumors per animal caused by diethylnitrosamine, a potent carcinogen, again, indicating an interaction.

The CPSC risk assessment made use of the multistage model which you heard Dr. Crump describe previously, which conforms to the widely held view by the scientific community that cancer development most likely occurs via a series of stages.

To conclude, Mr. Chairman, I believe that it is important to note that the risk assessment on formaldehyde from UFFI prepared by my staff was by no means a worst case. The basic assumptions were based on scientific principles that are generally accepted by the scientific community, and the exposure estimates were based on sound, real-life measurement. In fact, there is good reason to believe that our assessment may have underestimated the risk.

For a person living in a UFFI home under the conditions that we defined, the risk assessment predicted a risk of up to 51 chances in a million of developing cancer based on the methodology I described, but the assessment that we did was based only on malignant nasal, squamous cell carcinoma and did not include all of the data now available on benign tumors.

While it is not absolutely clear whether or not these benign tumors are precursors to the observed carcinomas, some experts—and you have heard one this morning—have testified that they may indeed be so.

Incorporation of the new data into the assessment would clearly raise the risk that we have predicted.

I do not want to imply by this—nor, hopefully, will you get the impression from me—that these are accurate and precise descriptors of risk. Rather, these are estimates that are the best that we can do based on current scientific knowledge and principles.

Significant public attention is now being focused on the issue of formaldehyde in hearings before this and other committees of Congress, in the Commonwealth of Canada, and before State bodies, and through the public statements of a number of scientists. We, for our part, intend to continue to work with the industry and with the public to develop solutions which will foster the continued, important commercial and scientific uses of formaldehyde in a sensibly safe fashion.

Mr. Chairman, I have appended several of the documents to which I referred in my formal testimony and offer them for inclusion in the record of this hearing.

This concludes my testimony, and I would be pleased to answer any questions you may have.

[The prepared statement of Dr. Preuss follows:]

# STATEMENT OF
PETER W. PREUSS PH.D.
ASSOCIATE EXECUTIVE DIRECTOR FOR HEALTH SCIENCES
U.S. CONSUMER PRODUCT SAFETY COMMISSION

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT
COMMITTEE ON SCIENCE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES

MAY 20, 1982

Mr. Chairman and members of the Committee, I am pleased to be here today to discuss with you the scientific issues regarding the health effects of formaldehyde. My name is Peter Preuss. I am the Associate Executive Director for Health Sciences at the Consumer Product Safety Commission.

As you know, on February 22, 1982, the U.S. Consumer Product Safety Commission voted to ban Urea Formaldehyde Foam Insulation, or "UFFI". The Commission took this step because of its concern about the health effects associated with formaldehyde and its belief that emission of formaldehyde from the foam could not be adequately controlled. The Commission was petitioned in 1976 to control the potential hazards associated with a a variety of insulations. During subsequent years, the Commission received over 2000 complaints from people who had installed UFFI in their homes and experienced acute symptoms such as irritation of the upper respiratory tract or of the eyes. As a part of the effort to understand these acute effects the Commission asked the National Academy of Sciences to review all the available information on the acute effects of formaldehyde and to make recommendations regarding the existence of a "tolerable" level of formaldehyde for indoor air. The Academy concluded that there was no population threshold for the irritant effects of formaldehyde. In addition, the Commission arranged a contract with the Franklin Research Institute to investigate the emission of formaldehyde from panels specially constructed to simulate the walls of homes and which had been insulated with UFFI by the major suppliers of the insulation. (This is referred to again in the discussion of exposure.) Finally, we held a series of public meetings around the country to obtain additional information

FROM INDUSTRY, ACADEMIA AND THE PUBLIC. THESE MEETINGS ELICITED IMPORTANT INFORMATION FROM THE PUBLIC, AND PERMITTED THE COMMISSIONERS TO MEET DIRECTLY WITH SOME OF THE INDIVIDUALS AFFECTED BY UFFI. IT WAS DURING THE COURSE OF THESE INVESTIGATIONS AND HEARINGS THAT THE FORMALDEHYDE INSTITUTE NOTIFIED US IN OCTOBER 1979 OF THE EARLY RESULTS OF THE CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY BIOASSAY EXPERIMENTS ON THE EFFECTS OF FORMALDEHYDE EXPOSURE. AT THAT TIME, THE FORMALDEHYDE INSTITUTE INFORMED US THAT THREE OF THE RATS EXPOSED TO 15 PARTS PER MILLION OF FORMALDEHYDE FOR 6 HOURS PER DAY, 5 DAYS PER WEEK, FOR ABOUT A YEAR, HAD BEEN FOUND TO HAVE NASAL CANCER. THIS RAISED A CONCERN ABOUT A POSSIBLE CANCER RISK TO LARGE SEGMENTS OF THE POPULATION BECAUSE MANY PEOPLE IN THIS COUNTRY WERE KNOWN TO BE EXPOSED TO FORMALDEHYDE.

SINCE THAT TIME, THERE HAS BEEN A GREAT DEAL OF DISCUSSION AND ANALYSIS (AS WELL AS CONTROVERSY) REGARDING THE CARCINOGENICITY OF FORMALDEHYDE. TO RESOLVE SOME OF THE ISSUES, THE COMMISSION ASKED FOR, AND RECEIVED, A REPORT FROM THE FEDERAL PANEL ON FORMALDEHYDE (FORMED UNDER THE AUSPICES OF THE NATIONAL TOXICOLOGY PROGRAM AND MADE UP OF GOVERNMENT SCIENTISTS)(GRIESEMER, 1982). IN ADDITION, THE CARCINOGENICITY OF FORMALDEHYDE HAS BEEN REVIEWED BY A WORKING GROUP OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC, 1982) AND BY AN INDEPENDENT PANEL AT THE MOUNT SINAI MEDICAL CENTER IN NEW YORK, WHO SUBMITTED A REPORT TO THE AMERICAN CANCER SOCIETY (I. SELIKOFF, ET AL. 1982). THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH HAS ALSO PUBLISHED A CURRENT INTELLIGENCE BULLETIN ON THE SUBJECT OF OCCUPATIONAL EXPOSURE TO FORMALDEHYDE (NIOSH, 1981). ALL OF THESE REVIEWS CAME TO THE

CONCLUSION THAT FORMALDEHYDE WAS A CARCINOGEN IN ANIMALS AND THAT IT SHOULD BE PRESUMED TO POSE A RISK OF CANCER TO HUMANS, OR THAT HUMAN EXPOSURE TO FORMALDEHYDE SHOULD BE REDUCED OR ELIMINATED. OF GREAT IMPORTANCE ARE THE STUDIES NOW ALMOST COMPLETED AT THE NEW YORK UNIVERSITY WHICH CONFIRM AND VALIDATE THE INDUSTRY EXPERIMENTS (ALBERT, ET AL. 1981), AS WELL AS VARIOUS EPIDEMIOLOGICAL STUDIES, SOME PRESENTLY IN PROGRESS, WHICH WE HOPE WILL SOON GIVE US A CLEARER PICTURE OF FORMALDEHYDE'S POSSIBLE CARCINOGENIC EFFECTS IN PEOPLE.

IN YOUR LETTER OF INVITATION TO ME YOU ASKED THAT I EVALUATE THE TOXICOLOGICAL DATA FROM ANIMAL STUDIES ON FORMALDEHYDE RELATED TO CARCINOGENICITY, THE APPLICATION OF THOSE ANIMAL DATA TO THE HUMAN SITUATION, AS WELL AS THE METHODS, PROCESSES AND ASSUMPTIONS THAT ARE A PART OF THE QUANTITATIVE ASSESSMENT OF POTENTIAL HUMAN RISK. AS A CONSEQUENCE, I HAVE EMPHASIZED THESE POINTS IN MY TESTIMONY TODAY. THIS IS NOT TO SAY, HOWEVER, THAT OTHER FACTORS WERE NOT CONSIDERED BY THE COMMISSION WHEN IT MADE ITS DECISION ON UFFI. IN FACT, BEFORE MAKING ANY RECOMMENDATIONS TO THE COMMISSION THE STAFF HAD THOROUGHLY INVESTIGATED AND REVIEWED A LARGE NUMBER OF ISSUES INCLUDING THE ACUTE EFFECTS OF FORMALDEHYDE, THE FEASIBILITY OF A STANDARD FOR UFFI, THE ECONOMICS OF VARIOUS ALTERNATIVE REGULATORY AND NON-REGULATORY OPTIONS, AS WELL AS THE POSSIBILITY OF CONSUMER REDRESS. AT YOUR REQUEST, HOWEVER, I WILL NOT TOUCH UPON THESE OTHER UFFI-SPECIFIC ISSUES, BUT WILL INSTEAD FOCUS ON THE QUESTION OF THE CARCINOGENICITY OF FORMALDEHYDE.

LET ME BEGIN WITH THE REASONS, GENERALLY, WHY I AM CONCERNED ABOUT THE

POTENTIAL CHRONIC EFFECTS OF FORMALDEHYDE. MY CONCERN IS BASED ON METABOLISM, MUTAGENICITY AND CARCINOGENICITY STUDIES (REVIEWED IN THE REPORT OF THE FEDERAL PANEL ON FORMALDEHYDE) (GRIESEMER, ET AL, 1982). IN BRIEF, THE BIOCHEMICAL STUDIES SHOW THAT FORMALDEHYDE REACTS READILY WITH OTHER CHEMICALS, INCLUDING PROTEINS AND NUCLEIC ACIDS. IT MAY ALSO BE CONVERTED TO FORMATE AND EXCRETED IN URINE, OR TO CARBON DIOXIDE AND EXHALED. THESE REACTIONS ARE SIMILAR IN LABORATORY ANIMALS AND MAN, ALTHOUGH THE REACTION RATES MAY VARY. BASED ON OUR PRESENT KNOWLEDGE OF FORMALDEHYDE BIOCHEMISTRY, FREE FORMALDEHYDE DOES NOT SEEM TO EXIST IN THE BODY.

FORMALDEHYDE IS ALSO MUTAGENIC IN BACTERIA, VIRUSES, FUNGI, INSECTS AND MOUSE LYMPHOMA CELLS WITH OR WITHOUT METABOLIC ACTIVATION. IT INDUCES CHROMOSOMAL RECOMBINATION IN YEAST, INSECTS, AND CULTURED MAMMALIAN CELLS, AS WELL AS CELLULAR TRANSFORMATION IN MOUSE BALB/C 3T3 CELLS (GRIESEMER, ET AL., 1980). THESE RESULTS INDICATE THAT FORMALDEHYDE IS CAPABLE OF BINDING TO, AND ALTERING, GENETIC MATERIAL.

EARLY STUDIES ON THE CARCINOGENIC POTENTIAL OF FORMALDEHYDE VIA INHALATION EXPOSURE (HORTON, 1963; DALBEY, 1980) WERE NEGATIVE, BUT SUFFERED FROM INADEQUATE EXPOSURE, TOO FEW ANIMALS, AND/OR INCOMPLETE PATHOLOGICAL EXAMINATION. THE RECENT STUDY BY THE CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY, WHICH I MENTIONED PREVIOUSLY, (CIIT, 1981) INVOLVED RATS AND MICE EXPOSED TO 0, 2, 6 AND 15 PPM OF FORMALDEHYDE FOR 6 HOURS/DAY, 5 DAYS/WEEK, FOR UP TO 24 MONTHS. AFTER 18 MONTHS OF EXPOSURE, A TOTAL OF 37 RATS EXPOSED TO 15 PPM OF FORMALDEHYDE HAD DEVELOPED NASAL, SQUAMOUS CELL CARCINOMA

(INITIAL CARCINOMAS APPEARED AT ABOUT 12 MONTHS). OTHER CHANGES OBSERVED DURING THIS STUDY WERE THE DEVELOPMENT IN RATS OF SQUAMOUS METAPLASIA, DYSPLASIA AND POLYPOID ADENOMA WHICH WERE DOSE RELATED. THE NUMBER OF RATS WITH SQUAMOUS CELL CARCINOMA INCREASED TO 103 IN THE 15 PPM EXPOSURE GROUP AFTER 24 MONTHS OF EXPOSURE. IN ADDITION, 2 RATS EXPOSED TO 6 PPM, AND 2 MICE EXPOSED TO 15 PPM, ALSO DEVELOPED SQUAMOUS CELL CARCINOMA OF THE NASAL CAVITY (CIIT, 1981).

SQUAMOUS CELL CARCINOMAS OF THE NOSE WERE ALSO OBSERVED IN ANOTHER STUDY IN WHICH RATS WERE EXPOSED TO AN AVERAGE OF 14 PPM OF FORMALDEHYDE AND 10 PPM OF HYDROGEN CHLORIDE (HCL) VAPOR (SELLAKUMAR, ET AL., 1980). IN SUCH A MIXTURE, THERE IS A POSSIBILITY OF THE FORMATION OF BIS (CHLOROMETHYL) ETHER, WHICH IS A KNOWN CARCINOGEN AND PRODUCES PRIMARILY ESTHESIO-NEUROEPITHELIOMAS OF THE NOSE AND SQUAMOUS CELL CARCINOMAS OF THE LUNG IN RATS (KUSCHNER, ET AL., 1975). THE PROJECTED LOW CONCENTRATION OF BIS (CHLOROMETHYL) ETHER OF LESS THAN 1 PART PER BILLION, LACK OF TUMORS TYPICAL OF BIS (CHLOROMETHYL) ETHER, THE SIMILARITY IN TYPE AND LOCATION OF TUMORS AS WELL AS SIMILARITIES IN THE CONCENTRATION OF FORMALDEHYDE BETWEEN THE TWO STUDIES - CIIT AND NYU - MAKE IT LIKELY THAT FORMALDEHYDE WAS THE PRIMARY CARCINOGEN.

A NEW STUDY AT NEW YORK UNIVERSITY IS CURRENTLY BEING COMPLETED IN WHICH RATS WERE EXPOSED TO 14 PPM OF FORMALDEHYDE, WITH AND WITHOUT 10 PPM HCL, AND 10 PPM HCL ALONE. SQUAMOUS CELL CARCINOMA OF THE NASAL CAVITY HAS DEVELOPED IN ALL EXPOSURE GROUPS CONTAINING FORMALDEHYDE, WHILE NO NASAL CARCINOMAS HAVE BEEN OBSERVED IN THE HCL AND CONTROL GROUPS (ALBERT, ET AL., 1981). THESE

RESULTS FURTHER SUPPORT THE CONCLUSIONS REGARDING THE CARCINOGENIC POTENTIAL OF FORMALDEHYDE.

AT THE PRESENT TIME, THE AVAILABLE EPIDEMIOLOGICAL STUDIES OF HUMANS EXPOSED TO FORMALDEHYDE VAPOR ARE INADEQUATE TO ASSESS ITS CARCINOGENIC POTENTIAL. IN ONE OF THESE STUDIES, WONG IDENTIFIED SOME 2,000 CHEMICAL WORKERS POTENTIALLY EXPOSED TO FORMALDEHYDE AND DESCRIBED THE CAUSE OF DEATH OF THE 146 WORKERS WHO DIED (WONG, 1980). MARSH IDENTIFIED APPROXIMATELY 2500 CHEMICAL WORKERS, AND ANALYZED THE CAUSES OF DEATH OF THE 115 WORKERS WHO HAD DIED (MARSH, 1980). WALRATH AND FRAUMENI, OF THE NATIONAL CANCER INSTITUTE, STUDIED SOME 1100 EMBALMERS WHO HAD DIED (WALRATH, ET AL., 1981). IN THESE STUDIES, EXCESS NASAL CANCER WAS NOT DETECTED. HOWEVER, A PRELIMINARY REPORT ON THE COHORT STUDIED BY THE NCI HAS NOTED A SIGNIFICANT INCREASE IN SKIN CANCERS, AS WELL AS AN INCREASE IN CANCER OF THE BRAIN. IT IS NOT CLEAR AT THIS TIME, WHETHER OR NOT THESE CANCERS ARE ASSOCIATED WITH EXPOSURE TO FORMALDEHYDE. THERE ARE, IN ADDITION, TWO STUDIES INVOLVING PATHOLOGISTS THAT HAVE PRODUCED CONFLICTING RESULTS. THE FIRST, A COHORT OF SOME 2000 PATHOLOGISTS, OF WHOM 181 HAD DIED, REVEALED NO INCREASE IN CANCER. THE SAME WAS TRUE FOR 154 PATHOLOGY TECHNICIANS WHO HAD DIED. A SECOND STUDY COMPARED PATHOLOGISTS TO RADIOLOGISTS AND FOUND INCREASED CANCER OF THE LUNG AND LYMPHATIC SYSTEM IN THE PATHOLOGISTS.

THESE STUDIES, HOWEVER, ALL SUFFER FROM PROBLEMS WHICH PREVENT THEM FROM COMING TO ANY DEFINITIVE CONCLUSIONS REGARDING THE CARCINOGENIC POTENTIAL OF FORMALDEHYDE IN HUMANS. THESE INCLUDE:

(1) THE STUDIES WERE NOT LARGE ENOUGH, AND THEREFORE STATISTICALLY POWERFUL ENOUGH, TO BE SURE OF THE ABILITY TO DETECT A SIGNIFICANT CARCINOGENIC RESPONSE;

(2) THE DURATION AND AMOUNT OF (CONCENTRATION IN AIR OF) EXPOSURE IS NOT KNOWN;

(3) COHORTS WERE NOT ALWAYS FOLLOWED LONG ENOUGH TO ALLOW CANCER TO DEVELOP;

(4) IT IS NOT CLEAR IF ALL WORKERS OF THESE COHORTS WERE KNOWN TO ACTUALLY HAVE BEEN EXPOSED TO FORMALDEHYDE.

A NEW ATTEMPT TO EVALUATE THE POTENTIAL HUMAN CARCINOGENICITY OF FORMALDEHYDE VAPOR HAS NOW BEEN STARTED BY THE NATIONAL CANCER INSTITUTE AND WILL INCLUDE SOME 17,000 WORKERS THOUGHT TO HAVE BEEN EXPOSED TO FORMALDEHYDE. IT IS HOPED THAT THE RESULTS WILL BE AVAILABLE IN TWO TO THREE YEARS.

ALTHOUGH EPIDEMIOLOGIC EVIDENCE FOR THE CARCINOGENICITY OF FORMALDEHYDE IN HUMANS IS INCONCLUSIVE AT PRESENT, A NUMBER OF INDEPENDENT REVIEWERS, INCLUDING THE FEDERAL PANEL ON FORMALDEHYDE, HAVE CONCLUDED THAT FORMALDEHYDE SHOULD BE PRESUMED TO POSE A CARCINOGENIC RISK TO HUMANS. THEIR CONCLUSION WAS BASED ON THE METABOLISM AND CARCINOGENICITY STUDIES I HAVE DISCUSSED, AS WELL AS OTHER TESTS WHICH INDICATE THAT FORMALDEHYDE REACTS DIRECTLY WITH DNA IN THE NUCLEUS OF THE CELL, AND INDUCES MUTATIONS IN BOTH MAMMALIAN AND NON-

MAMMALIAN CELLS, AND CELL TRANSFORMATION IN MAMMALIAN CELLS.

A SECOND, INDEPENDENT, PANEL AT MOUNT SINAI MEDICAL CENTER (SELIKOFF ET AL., 1981) HAS RECOMMENDED THAT EFFORTS SHOULD BE MADE TO REDUCE OR ELIMINATE HUMAN EXPOSURE TO FORMALDEHYDE. MORE RECENTLY, DR. ARTHUR UPTON, FORMER DIRECTOR OF THE NATIONAL CANCER INSTITUTE AND PROFESSOR AND CHAIRMAN OF THE NEW YORK UNIVERSITY INSTITUTE OF ENVIRONMENTAL MEDICINE, HAS WRITTEN THAT FORMALDEHYDE IS DECISIVELY CARCINOGENIC IN ANIMALS AND WITH THE EVIDENCE FOR ITS GENOTOXICITY, IT IS LIKELY THAT FORMALDEHYDE IS A HUMAN CARCINOGEN. WHILE THE RELATIVE POTENCY FOR ANIMALS AND HUMANS IS UNCERTAIN, HE HAS WRITTEN THAT IT WOULD BE A MISTAKE TO IGNORE THE EVIDENCE FOR CARCINOGENCITY ON THE GROUNDS OF NEGATIVE EPIDEMIOLOGY, WHICH AT BEST CAN ONLY SET UPPER LIMITS TO THE CARCINOGENIC POTENCY IN HUMANS. DR. UPTON STATED THAT IF THE CARCINOGENICITY OF FORMALDEHYDE WERE TO BE IGNORED, IT WOULD MEAN THAT NO AGENT COULD BE REGARDED AS CARCINOGENIC IN THE ABSENCE OF POSITIVE EVIDENCE IN HUMANS. HE RECOMMENDED THAT FEDERAL REGULATORY AGENCIES SHOULD REGARD FORMALDEHYDE AS A CARCINOGEN AND FIND WAYS TO CONTINUE ITS IMPORTANT COMMERCIAL AND SCIENTIFIC USES IN A SENSIBLY SAFE FASHION (UPTON, 1981).

FINALLY, IT SHOULD BE NOTED THAT A WORKING GROUP APPOINTED BY THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, A PART OF THE WORLD HEALTH ORGANIZATION, CONCLUDED THAT:

> "THE EPIDEMIOLOGICAL STUDIES PROVIDE INADEQUATE EVIDENCE TO ASSESS THE CARCINOGENICITY OF FORMALDEHYDE TO MAN. IN THE ABSENCE OF ADEQUATE

EPIDEMIOLOGICAL DATA, FORMALDEHYDE GAS SHOULD BE CONSIDERED, FOR PRACTICAL PURPOSES, AS IF IT REPRESENTED A CARCINOGENIC RISK TO MAN" (IARC, 1981).

THE SECOND CRITICAL FACET IN THE ASSESSMENT OF HUMAN RISK IS THE DETERMINATION OF EXPOSURE TO THE CHEMICAL, AS CLEARLY, THE DEGREE OF RISK IS RELATED BOTH TO THE EXTENT AND THE DURATION OF EXPOSURE TO THE CHEMICAL IN QUESTION.

THE CPSC BECAME INVOLVED WITH HUMAN EXPOSURE TO FORMALDEHYDE BECAUSE OF THE EMISSION OF FORMALDEHYDE FROM A PARTICULAR CONSUMER PRODUCT, UREA-FORMALDEHYDE FOAM INSULATION (UFFI). AS I HAVE MENTIONED BEFORE, THE AGENCY WAS CONCERNED ABOUT BOTH THE ACUTE AND CHRONIC EFFECTS OF FORMALDEHYDE RELEASED FROM UFFI, AS WELL AS THE INABILITY OF THE INDUSTRY TO PREPARE A PRODUCT THAT WOULD MEET A FEASIBLE STANDARD. THE COMMISSION'S INVOLVEMENT WITH UFFI LED TO AN EXTENSIVE ANALYSIS OF EXPOSURE FOR THIS PRODUCT. THE COMMISSION STAFF EVALUATED MEASUREMENTS OF FORMALDEHYDE IN OVER 1100 HOMES WITH UFFI AND 100 HOMES WITHOUT UFFI. WE FOUND THAT THE HIGHEST LEVELS OF FORMALDEHYDE IN UFFI HOMES TEND TO OCCUR IMMEDIATELY AFTER INSTALLATION, AVERAGING BETWEEN 0.2 AND 0.3 PPM SOME TIME AFTER INSTALLATION, AND THAT THE AVERAGE LEVEL DECLINES RAPIDLY, FALLING TO BELOW 0.1 PPM AFTER A YEAR. THEREAFTER, THE AVERAGE LEVEL IN UFFI HOMES TENDS TO DECLINE RATHER SLOWLY OVER A PERIOD OF YEARS, APPROACHING A BACKGROUND LEVEL WHICH IS APPROXIMATELY 0.03 PPM.

The exposure pattern just described has been observed in two other studies as well. The first was conducted by the Nassau County Department of Health, in which over 50 UFFI homes were measured. They noted a similar rapid decline over the first year followed by a gradual decrease thereafter. The other study was conducted by the Franklin Institute Research Laboratory, the Oak Ridge National Laboratory and the CPSC. Panels simulating the exterior and interior walls of a home were constructed and foamed under conditions of the best available technology by manufacturer's representatives. In all cases, formaldehyde was released into that portion of the panel representing the indoor environment. Modeling by the Oak Ridge National Laboratory predicted indoor formaldehyde levels, based on panel measurements, similar to those actually measured in UFFI homes. Of equal importance, the study reproduced the observation of a rapid initial decline of formaldehyde level as the foam ages (Osborn, et al. 1980, 1981).

Once exposure is established and the determination has been made that formaldehyde has the potential to pose a carcinogenic risk to humans, the process of risk assessment can be invoked. The risk assessment calculated by CPSC included a number of assumptions dealing with extrapolations between animal species and from high to low doses, the proportion of lifetime that the animals were exposed vs. the proportion of lifetime that people might be exposed, as well as ideas about the way in which formaldehyde exposure might give rise to tumors. One aspect of the risk assessment that deserves special mention, however, is our use of a methodology that includes a linear component at low doses. We have used such a methodology, in addition to a

"BEST-FIT-OF-DATA" METHODOLOGY, BECAUSE OF THE FORMER'S GREATER BIOLOGICAL PLAUSIBILITY. MANY SCIENTIFIC PAPERS HAVE BEEN WRITTEN ON THE SUBJECT OF RISK ASSESSMENT POINTING OUT THAT THE SHAPE OF THE DOSE RESPONSE CURVE WOULD BE LINEAR AT LOW DOSES IF A CARCINOGEN WERE TO ACT IN A MANNER THAT WOULD BE ADDITIVE TO THE ACTION OF OTHER CARCINOGENS OR OTHER BACKGROUND CARCINOGENIC PROCESSES IN THE BODY.

IN THE CPSC FORMALDEHYDE RISK ASSESSMENT, THERE IS A DISCUSSION OF WHY THE INTERACTION OF FORMALDEHYDE WITH OTHER ENVIRONMENTAL CARCINOGENS AND BACKGROUND PROCESSES IS MORE LIKELY THAN THE PREMISE OF FORMALDEHYDE ACTING INDEPENDENTLY. THE REASONS INCLUDE THE FACT THAT FORMALDEHYDE, LIKE MANY OTHER CARCINOGENS, CAN CAUSE GENETIC DAMAGE BY MUTATION. SEVERAL STUDIES HAVE SHOWN THAT FORMALDEHYDE CAN ENHANCE THE EFFECT OF OTHER MUTAGENIC AGENTS, INDICATING THAT AN INTERACTION IS OCCURRING (GRIESEMER, 1982). THERE IS ALSO A STUDY IN ANIMALS IN WHICH FORMALDEHYDE WAS SHOWN TO INCREASE THE NUMBER OF TUMORS PER ANIMAL CAUSED BY DIETHYLNITROSAMINE, A POTENT CARCINOGEN, AGAIN INDICATING AN INTERACTION (DALBEY, 1980). THE CPSC RISK ASSESSMENT MADE USE OF THE MULTISTAGE MODEL WHICH CONFORMS TO THE WIDELY HELD VIEW BY THE SCIENTIFIC COMMUNITY THAT CANCER DEVELOPMENT MOST LIKELY OCCURS VIA A SERIES OF STAGES.

I SHOULD EMPHASIZE, AGAIN, THAT THE CARCINOGENICITY OF FORMALDEHYDE WAS NOT THE ONLY FACTOR THAT WAS CONSIDERED BY THE COMMISSION IN ARRIVING AT ITS DECISION ON UFFI. OTHER FACTORS THAT WERE IMPORTANT COMPONENTS OF THE DECISION INCLUDED ACUTE HEALTH EFFECTS, FEASIBILITY OF A STANDARD, AND THE

ECONOMIC IMPACTS OF A BAN AND OTHER ALTERNATIVES.

TO CONCLUDE, MR. CHAIRMAN, I BELIEVE THAT IT IS IMPORTANT TO NOTE THAT THE RISK ASSESSMENT ON FORMALDEHYDE FROM UFFI PREPARED BY MY STAFF WAS BY NO MEANS A "WORST CASE." THE BASIC ASSUMPTIONS WERE BASED ON SCIENTIFIC PRINCIPLES THAT ARE GENERALLY ACCEPTED BY THE SCIENTIFIC COMMUNITY, AND THE EXPOSURE ESTIMATES WERE BASED ON SOUND, REAL-LIFE MEASUREMENTS. IN FACT, THERE IS GOOD REASON TO BELIEVE THAT OUR ASSESSMENT MAY HAVE UNDERESTIMATED THE RISK. FOR A PERSON LIVING IN A UFFI HOME UNDER THE CONDITIONS DEFINED, THE RISK ASSESSMENT PREDICTED A RISK OF UP TO 51 CHANCES IN A MILLION OF DEVELOPING CANCER BASED ON THE METHODOLOGY I DESCRIBED. BUT THE ASSESSMENT IS BASED ONLY ON MALIGNANT NASAL SQUAMOUS CELL CARCINOMA, AND DOES NOT INCLUDE ALL OF THE DATA NOW AVAILABLE ON BENIGN TUMORS. WHILE IT IS NOT ABSOLUTELY CLEAR WHETHER OR NOT THESE BENIGN TUMORS ARE PRECURSORS TO THE OBSERVED CARCINOMA, SOME EXPERTS HAVE TESTIFIED THAT THEY MAY INDEED BE SO. INCORPORATION OF THESE NEW DATA INTO THE ASSESSMENT WOULD CLEARLY RAISE THE RISK PREDICTED.

I DO NOT WANT TO IMPLY BY THIS, NOR, HOPEFULLY, WILL YOU GET THE IMPRESSION FROM ME, THAT THESE ARE ACCURATE AND PRECISE DESCRIPTORS OF RISK. RATHER, THESE ARE ESTIMATES THAT ARE THE BEST THAT WE CAN DO, BASED ON CURRENT SCIENTIFIC KNOWLEDGE AND PRINCIPLES.

IN CONCLUSION, I WOULD ONCE MORE POINT TO THE PATH THAT WE HAVE FOLLOWED TO SUPPORT OUR EFFORTS TO ASSESS THE HEALTH EFFECTS OF FORMALDEHYDE. WHEN

ACUTE, SHORT-TERM EFFECTS WERE OUR MAJOR CONCERN, WE WENT TO THE NATIONAL ACADEMY OF SCIENCES AND ASKED THEM TO EVALUATE THE LITERATURE FOR US IN THAT AREA. WHEN WE BECAME CONCERNED ABOUT THE CHRONIC, LONG-TERM EFFECTS, WE WENT TO THE NATIONAL TOXICOLOGY PROGRAM, ESTABLISHED THE FEDERAL PANEL ON FORMALDEHYDE AND ASKED THEM TO EVALUATE THE LITERATURE AND DATA ON CANCER, BIRTH DEFECTS AND MUTAGENICITY, AS WELL AS ALL OTHER DATA ON CHRONIC EFFECTS. WHEN OTHER AGENCIES SUBSEQUENTLY BECAME CONCERNED, THE INTERAGENCY REGULATORY LIAISON GROUP TASK GROUP WAS ESTABLISHED TO FOSTER A COORDINATED, COMPREHENSIVE AND COHERENT APPROACH TO THIS ISSUE.

SIGNIFICANT PUBLIC ATTENTION IS NOW BEING FOCUSED ON THE ISSUE OF FORMALDEHYDE, IN HEARINGS BEFORE THIS AND OTHER COMMITTEES OF THE CONGRESS, IN THE COMMONWEALTH OF CANADA AND BEFORE STATE BODIES, AND THROUGH THE PUBLIC STATEMENTS OF SCIENTISTS SUCH AS DR. ARTHUR UPTON, DR. SELIKOFF AND OTHERS. WE, FOR OUR PART, INTEND TO CONTINUE TO WORK WITH THE INDUSTRY AND WITH THE PUBLIC TO DEVELOP SOLUTIONS WHICH WILL FOSTER THE CONTINUED IMPORTANT COMMERCIAL AND SCIENTIFIC USES OF FORMALDEHYDE, IN A SENSIBLY SAFE FASHION.

MR. CHAIRMAN, I HAVE APPENDED SEVERAL OF THE DOCUMENTS TO WHICH I REFERRED IN MY FORMAL TESTIMONY AND REQUEST THAT THEY BE INCLUDED IN THE RECORD OF THIS HEARING.

THIS CONCLUDES MY FORMAL TESTIMONY. I WOULD BE PLEASED TO ANSWER ANY QUESTIONS.

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Mr. GORE. Thank you.

Without objection, that material will be put into the record. (See appendix 4.)

Let me ask you first whether you are familiar with the memorandum that we have discussed this morning prepared by Dr. Todhunter.

Dr. PREUSS. I am.

Mr. GORE. Is there anything in that memorandum which would convince you to change your recommendation to the Consumer Product Safety Commission that resulted in the ban on urea formaldehyde foam?

Dr. PREUSS. The Commission decision on urea formaldehyde foam insulation was based, not only on the potential carcinogenic effects of formaldehyde in humans, but on a large number of other factors—the acute effects of formaldehyde, the possibility of a standard, and so forth.

To answer your question directly however, there is not anything in that memorandum that would have caused me to change my recommendation as a scientist to the Commission.

Mr. GORE. The CPSC decision—your Commission's decision—was on February 22. The memorandum prepared by Dr. Todhunter is dated February 10. Were you consulted prior to the issuing of that memorandum by Dr. Todhunter?

Dr. PREUSS. No, I was not.

Mr. GORE. How did the CPSC learn about the Todhunter decision?

Dr. PREUSS. The memorandum came to our attention as part of a submission by the Formaldehyde Institute for the public record of the hearing that was considering UFFI.

Mr. GORE. What date?

Dr. PREUSS. I do not recall exactly. It was the week after February 10—perhaps February 18 or 19.

Mr. GORE. I see.

Has it been usual in the past for the scientific parts of these various agencies to consult with one another on substances that are under review?

Dr. PREUSS. Yes, it has, sir.

Mr. GORE. There was an interregulatory agency liaison group formed to coordinate the Government's study of this formaldehyde issue; is that correct?

Dr. PREUSS. Yes, there was.

Mr. GORE. What happened to that?

Dr. PREUSS. Dr. Ulsamer, who sits next to me, was the chairman of that group. It was set up under the aegis of the Interagency Regulatory Liaison Group to try and prepare an integrated assessment, for all of the agencies, of the risks attendant to formaldehyde and to recommend priorities to each of the agencies as to how to proceed.

With the change in administration, the new heads of the agencies felt that there were better ways, perhaps, of doing things than the IRLG, and so the IRLG was not continued past, I believe, last September.

Mr. GORE. It seemed to me to be a waste of the taxpayers' money to require all of these separate agencies to redo all the work all over again without coordinating with each other. I will not ask you to comment on that, but it certainly seems that those of us in the Congress ought to look at that as a possible waste of the taxpayers' money.

Dr. PREUSS. Mr. Chairman, I do not mean to imply by that that there is no communication among agencies at this point. My staff are in constant touch with staff from other agencies, and we discuss a variety of issues. There are still a variety of working groups that are going on, so that communications do continue.

Mr. GORE. But there was no such communication prior to the February 10 memorandum of Dr. Todhunter?

Dr. PREUSS. Not specifically with regard to the memorandum, no.

Mr. GORE. All right.

The National Research Council report on formaldehyde expressed concern that many different methods had been used to measure formaldehyde. Dr. Todhunter, in his February 1982 memorandum to the EPA Administrator also expressed concern about the use of different methods for determining the concentration of formaldehyde. Have you and your staff assessed the various methods for determining formaldehyde?

Dr. PREUSS. We have. There are indeed a large number of methods that can be used and that have been used occasionally. The largest number of measurements have, however, been done by one or two methods. The most prevalent method that recommended by NIOSH, which is the chromotropic acid procedure.

For example, when we looked at the analyses and the tests that had been done to prepare for the UFFI decision, we went through all of the tests and found that the vast majority were done by the chromotropic acid method.

Mr. GORE. Do you agree generally with the scientific assessments of this memorandum that came from the previous panel?

Dr. PREUSS. I do.

Mr. GORE. With respect to epidemiology, it seems that the generally accepted view of the epidemiological studies is that they are not adequate to give us an answer one way or the other. Would you agree with that view?

Dr. PREUSS. You mean those that have been done so far?

Mr. GORE. The epidemiology studies that have been done are inadequate to tell us whether or not formaldehyde is a carcinogen in humans.

Dr. PREUSS. Yes, I agree with that.

Mr. GORE. Todhunter memorandum states it differently. I quote:

> Three epidemiology studies presented at CIIT are in agreement that there is no excess in nasal or respiratory cancer or even a significant increase in any form of cancer which could be attributed to formaldehyde. Although the individual studies may be limited in scope, when combined they clearly indicate no increased risk in the exposed population.

That is a little different from the view that you expressed earlier.

What is the level of risk to the general public from formaldehyde exposure that accompanied or triggered the CPSC regulatory action?

Dr. PREUSS. I assume you are referring to the carcinogenic risk that we calculated?

Mr. GORE. Yes. At what level?

Dr. PREUSS. In our exposure work we found that the average level of formaldehyde in homes that had been treated with this insulation was slightly above 0.1 part per million. When we calculated the risk to the people living in those homes over a period of 9 years, which was as far out as our data extended, the calculation was up to 51 parts per million.

Mr. GORE. OK, very good.

I would like to recognize counsel for the minority.

Mr. CLEMENT. Thank you, Mr. Chairman.

Dr. Preuss, I am somewhat concerned here on one thing, and that is, we seem to be concentrating exclusively on the problem of carcinogenicity in formaldehyde. In fact, we are really talking about apples and oranges here, are we not? You were regulating urea foam formaldehyde insulation, and the question at the Environmental Protection Agency is formaldehyde as a generic chemical; is that not correct?

Dr. PREUSS. It is correct that we dealt with urea formaldehyde foam insulation as a specific product, that there were many other considerations that entered into it other than the carcinogenicity of formaldehyde.

Mr. CLEMENT. In fact, the Consumer Product Safety Commission commenced its action on urea foam formaldehyde insulation before the question of human carcinogenicity came up; is that not true?

Dr. PREUSS. That is correct.

Mr. CLEMENT. Were not the original consumer questions that got you involved in UFFI involved with acute sensitivity in humans that were exposed within the home environment?

Dr. PREUSS. Yes, sir.

Mr. CLEMENT. And in fact you could and would have regulated on UFFI based solely on those acute sensitivity reactions; is that not true?

Dr. PREUSS. It is difficult to answer, because I cannot speak for the minds of five Commissioners as to what they would have done.

Mr. CLEMENT. The Commission could have—let me rephrase it.

Dr. PREUSS. Not being a lawyer, I would say yes, but do not hold me to it.

Mr. CLEMENT. All right.

Mr. GORE. That is a regulatory decision, but of course you may proceed.

Mr. CLEMENT. There is a rather significant difference between the enabling statute under which CPSC regulates and those under which EPA regulates; is that correct?

Dr. PREUSS. Again, you will forgive me; I am not entirely familiar with the EPA enabling statutes. I am familiar with the statutes under which CPSC functions.

Mr. CLEMENT. The Consumer Product Safety Act allows you to regulate consumer products?

Dr. PREUSS. Yes, sir.

Mr. CLEMENT. All right. Whereas EPA deals in much broader areas and does not deal with individual products but with overall environmental impacts; is that your understanding?

Dr. PREUSS. In part. I believe that under the Toxic Substances Act, EPA does have authority to deal with consumer products or occupational hazards or other hazards should the occasion warrant, but there are provisions within that act for consultation and working with the other agencies.

Mr. **Clement**. Let me ask, is it necessary for your Commission to get cancer data from animal tests before the Commission would act to ban consumer products that the Commission thought was unsafe?

Dr. **Preuss**. No. The statutory requirement that the Consumer Product Safety Commission faces is the finding of an unreasonable risk, which is based on health data, which may or may not have anything to do with carcinogenicity; it has to do with the costs of such an action as well as many other factors.

Mr. **Clement**. And I believe you have already testified that you first began looking at UFFI before there was a question of it being a human carcinogen.

Dr. **Preuss**. That is correct.

Mr. **Clement**. That is correct. All right. So you were looking at it because of its acute effects, such as headaches or the problems with drying of the mucous membranes and other uncomfortable health responses in human beings that are exposed to formaldehyde that was out-gassing from the UFFI?

Dr. **Preuss**. Yes, we were doing all of that before the information about carcinogenicity became available.

Mr. **Clement**. My understanding of your process was that, at the time you were looking into the UFFI question, the problem, as I recall it, was that installers on the scene mixed chemicals in a machine that that injected it into the walls, and that the problem most frequently found was that untrained or unskilled installers were adding, instead of perhaps one X formaldehyde that was necessary for the proper application were adding up to twice as much because it made no great difference to the foam itself, and therefore there was excess formaldehyde in the mix that would then out-gas; is that correct?

Dr. **Preuss**. Part of it is correct; that is that the formaldehyde foam material was made onsite and then pumped into the house by the installer. I am not sure that I could agree with you as to the reasons that formaldehyde was being given off into the inner spaces of people's homes.

In fact, one of the things that we tried to do to answer this question was the study that I referred to at the Franklin Institute, where we had the installers come in and foam panels for us, using the best technology that they could. Even under those circumstances, formaldehyde was emitted into the interior space.

Mr. **Clement**. All right. I do have one final question, and that is, I do not completely understand the out-gassing process, but my reading leads me to believe that there is a very definite curve, particularly with improper applications.

It looks like Dr. Ulsamer may have some information in this area, but I understand that the curve starts quite high immediately after application, as the free formaldehyde out-gasses, and then falls off rather dramatically. Is that correct over a rather short period of time, Dr. Ulsamer?

Dr. **Ulsamer**. It depends on what you mean by "short period of time." The levels of formaldehyde that come off during the first year—say, after the foam is put in—are relatively high, and then the curve drops off fairly quickly and sort of runs down toward the baseline.

Mr. **Clement**. Let me ask you at this point—either Dr. Ulsamer or Dr. Preuss—would you in fact advise someone who has a home that has UFFI in it, that was put in it several years ago—3, 4, or 5 years ago—where the amount of formaldehyde out-gassing is very low, as Dr. Ulsamer has indicated—what would your advice be to the homeowner who was in that position?

Dr. **Preuss**. I think that would depend in large part on a number of factors. The first is whether or not that homeowner was experiencing any symptoms of acute distress.

Mr. **Clement**. Presuming they were not experiencing symptoms of an acute sensitivity reaction of some kind—they had no symptoms—what would your advice be?

Dr. **Preuss**. Again, if they were concerned about the possible effects of formaldehyde coming from the foam and they were not experiencing acute effects, I would advise them to try and get a sample of the air in the house to see what kinds of levels of formaldehyde were present.

If it has been 3, or 4, or 5 years after the installation of the foam, our data seem to indicate that at that point it is approaching in many cases, or perhaps in most cases, the background level of formaldehyde that is likely to be present in any house, and if that is the case, my advice would be to do nothing.

Dr. **Ulsamer**. I should caution—when I made my statement—that those are average circumstances.

Mr. **Clement**. I understand.

Dr. **Ulsamer**. Individual homes may vary quite significantly.

Mr. **Clement**. Your explanation is in very close correlation with my understanding. Would you agree with Dr. Preuss that, if they are not experiencing any acute sensitivity reactions, they have no great cause for concern?

Dr. **Ulsamer**. Individual susceptibility to the so-called acute effects of formaldehyde can vary quite substantially from one individual to another, just as the release of the formaldehyde can vary depending on the temperature, the air exchange rate in the house, et cetera.

If the individual had a concern even 4 or 5 years after, he should have a measurement taken.

Mr. **Clement**. But the mere fact that the UFFI is there, if it is not out-gassing badly and they are not suffering the acute reaction, then you would concur with Dr. Preuss that there is no particular problem?

Dr. **Ulsamer**. If the UFFI is not off-gassing formaldehyde to any significant amount, no, there would not be a problem.

Mr. **Clement**. Let me ask you one last question. That is, in fact under the Consumer Product Safety Act, Dr. Preuss, when the Commission is considering a consumer product for regulation or banning, the Commission can and should consider whether or not there are alternatives to that product available to the consumer and the economic consequences; is that true?

Dr. **Preuss**. Yes, sir.

Mr. CLEMENT. I would like to read you—well, I am not going to read you, because I do not have it at hand, but I will go from memory, if my chairman will allow me. Under section 4(f) of TSCA, the EPA Administrator is required, upon receipt of information that a chemical poses a signficant human risk due to carcinogenicity, due to birth defects, or due to chromosomal damage, to propose a chemical for regulation within 180 days. That is a considerably different mandate than the one you have under the Consumer Product Safety Act; is that correct?

Dr. PREUSS. From what you are saying, yes, sir.

Mr. CLEMENT. I have no further questions, Mr. Chairman.

Mr. GORE. The fact is that, even though you could have made your recommendation based solely on the acute effects, in fact your recommendation was based on the carcinogencity as well; is that correct?

Dr. PREUSS. Yes, sir.

Mr. GORE. All right. That is why you asked the NTP panel to review the data; is that correct?

Dr. PREUSS. We asked the NTP to set up the panel to evaluate all of the data on chronic health effects, including the carcinogencity, because we felt it was an important component of the decision.

Mr. GORE. All right.

When you were looking at the carcinogenicity issue, what risk levels were you looking at when you made your decision on the extrapolation from animal studies?

Dr. PREUSS. As I mentioned, the risk assessment that we prepared indicated that for the specific set of circumstances of people living in these homes for up to 9 years, the risk we calculated was up to 51 in a million—1 in 20,000 approximately.

Mr. GORE. What is that as 10 to the minus?

Dr. PREUSS. That is 2 times 10 to the −4.

Mr. GORE. Was that 2 times 10 to the −4?

Dr. PREUSS. I am sorry—2 times 10 to the −3—wait a moment—I was right; it is 2 times 10 to the −4.

Mr. GORE. All right; great; I am glad some other people get mixed up with this.

I have two quick questions before we go on. There was one dissenter to the CPSC decision, Commissioner Statler. He said in his decision—did he not?—that he would not put UFFI foam in his house.

Dr. PREUSS. Yes, he did.

Mr. GORE. One final question: Was it possible to demonstrate a statistically significant difference in the exposure levels in homes with UF foam as compared to homes that did not have UF foam?

Dr. PREUSS. Yes. In fact this was a major point of contention during our discussion, in that the industry indicated that there was not a difference. We looked at all of the data that we had available to us—some 1,200 homes—and found that there was indeed a strong, statistically significant difference between homes with UFFI and homes without. In addition, the Canadian Government did a rather large study on the same issue and came to the same conclusion that there was a difference.

Mr. GORE. That is interesting. Another part of Dr. Todhunter's memo says—and I quote—"It has not been possible to demonstrate a statistically significant difference in exposure levels in UF foam homes as opposed to non-UF homes." That is just wrong, is it not?

Dr. **Preuss**. It is incorrect.

Mr. **Gore**. Thank you very much, and thanks to all of our witnesses.

I would like to call now Dr. John Todhunter, Assistant Administrator for Pesticides and Toxic Substances with the Environmental Protection Agency.

Are your colleagues going to give testimony as well?

Mr. **Todhunter**. No. They will answer questions.

Mr. **Gore**. If all three of you then would raise your right hands—do you solemnly swear the testimony you are about to give will be the truth, the whole truth, and nothing but the truth, so help you God?

Dr. **Todhunter**. I do.

Mr. **Pedersen**. I do.

Mr. **Clay**. I do.

Mr. **Gore**. If you would identify your colleagues for the reporter and for the record——

Dr. **Todhunter**. I would be most happy to, Mr. Chairman. To my left is Mr. William Pedersen of the Office of General Counsel, U.S. Environmental Protection Agency. To my right is Mr. Donald Clay, the director of the Office of Toxic Substances, U.S. Environmental Protection Agency.

Mr. **Gore**. Without objection, the entire text of your prepared remarks will be inserted in full in the record.

Dr. **Todhunter**. Sir, my remarks are rather brief, and I would like to be able to present them orally.

Mr. **Gore**. That is fine.

## STATEMENT OF DR. JOHN TODHUNTER, ASSISTANT ADMINISTRATOR FOR PESTICIDES AND TOXIC SUBSTANCES, ENVIRONMENTAL PROTECTION AGENCY, ACCOMPANIED BY MR. DONALD CLAY, DIRECTOR, OFFICE OF TOXIC SUBSTANCES AND MR. WILLIAM PEDERSEN, OFFICE OF GENERAL COUNSEL

Dr. **Todhunter**. Mr. Chairman and members of the subcommittee, good afternoon. I welcome the opportunity to be here to discuss with you the status of the EPA's program on formaldehyde. The interest of the subcommittee is understandable, given the numerous misconceptions and misrepresentations which exist about our approach to formaldehyde. I believe firmly that once I have identified the nature of these misconceptions, the members of the subcommittee will understand that EPA's actions have been scientifically defensible and true to the intent of the Toxic Substances Control Act. I should like to address each of these misconceptions.

The first misconception is that the previous administration was proposing to regulate formaldehyde. In fact, at no time in the past did EPA propose to regulate formaldehyde. The previous administration proposed only to conduct a 2-year exposure analysis and risk assessment program. This program was to have started in 1981 at some point and to have ended around October 1983.

Now in fact this program, in a stronger and more expedited form, I might add, is presently being initiated by EPA. We are moving to establish several expert review panels to consider specific formaldehyde issues. These panels will be run under the auspices of the National Center for Toxicological Research, and will tap the scientific expertise of Government agencies, academia, and industry. We hope to hold a consensus-building workshop within 1 year and will be able to significantly improve the quality of our exposure and toxicological data well ahead of the previously proposed schedule.

The difference in our approach concerns the use of section 4-f of TSCA. Section 4-f itself is not a regulatory vehicle but rather a priority-setting mechanism. This section was placed in the law to insure that significant health risks from cancer, gene mutations, and birth defects receive priority action. This section of TSCA requires the exercise of judgment and is therefore a discretionary action on the part of the Administrator.

Section 4-f does require the Administrator to initiate rulemaking action within 180 days under sections 5, 6, or 7 of TSCA when the Administrator receives information that leads her to conclude, on a reasonable basis, that a significant risk of serious or widespread harm from cancer, gene mutations, or birth defects is presented or will be presented by a chemical substance. The statute does not authorize the use of section 4-f for just any risk.

The statute also does not say: "If it is 4-f, go out and spend 2 years investigating." It says: "Go out and regulate" unless you can make a finding within 180 days that the significant risk is not unreasonable. Regulations shall be under section 5 for new chemical substances, section 6 for hazardous chemical substance, or section 7 for imminent hazards.

It takes at least 6 months to develop a clear, defensible regulatory proposal. That means you must have a substantial amount of data in hand before you invoke section 4-f. Now this is a very important point. The concept of using an exposure investigation as a response to a section 4-f finding is contrary to the statute. Any documents which make such a recommendation are then irrelevant, as they propose actions contrary to law. Such recommendations must—the science entirely aside—be dismissed out of hand.

In summary, the question the agency faced was straightforward: Is the available evidence sufficient to point EPA toward expedited rulemaking or not? The answer to this question has always been no. That is why EPA in the past had proposed an exposure investigation to be done over 2 years. The agency very much needed reliable data on specific exposure situations then; it very much needs it now. That is why, as I have mentioned previously, we have refined the investigatory proposal, are carrying it out, and expect to bring in the necessary information one-half year ahead of what the previous administrations hoped to be able to do.

A listing of formaldehyde as a section 4-f chemical is at present inappropriate. You do not call something a "significant risk" and then say: "We need to get exposure data." The proper scientific approach would be to say: "We need exposure data," then to go out and get that data, and only then to make an intelligent, factually based decision concerning the use of section 4-f or any other section of TSCA, and that is what this administration is doing.

The second misconception is that EPA has somehow departed from longstanding principles of risk assessment in developing its position on formaldehyde. The fact is, EPA considers formaldehyde to be a carcinogen in the rat by the inhalation route, possibly also in the mouse by the same route, and EPA presumes that formaldehyde may, in theory, pose a risk of cancer to humans. EPA also holds that animal testing, carefully analyzed, is an appropriate indicator of potential human risk.

Now whether or not a substance may pose any risk of cancer to humans, however, is not the issue under TSCA section 4-f. The question is whether or not the cancer risk is significant. The question is, simply put: Is this a high degree of risk or a low degree of risk?

The answer to that question depends intimately on exposure. The exposure information presently available to OTS indicates that carcinogenic risk for most, if not all uses of formaldehyde is in a range that regulatory agencies normally would consider low. Indeed, the estimated risks are in the range that regulatory agencies often seek to achieve when they impose controls. At these low-risk ranges one would not expect to actually find any detectable excess of tumors in the population at risk. One of our panelists earlier this morning quite clearly came back with the concept that 10 to 4 was certainly acceptable to him in the occupational setting.

Allow me to quote from the dissenting opinion on the urea formaldehyde insulation ban of Consumer Product Safety Commissioner Stuart M. Statler:

> * * * CPSC staff confirm that formaldehyde is regarded as a relatively weak carcinogen. Hence, the probability of cancer risk associated with exposure to formaldehyde gas appears considerably less than the risks from other known cancer-causing agents. By way of comparison, the very same Canadian government which barred urea formaldehyde foam identifies the added cancer risk associated with 0.1 ppm formaldehyde exposure comparable to smoking only one-third of a cigarette daily.

We must not forget that CPSC originally became interested——

Mr. GORE. Dr. Todhunter, you were quoting from Mr. Statler?

Dr. TODHUNTER. Yes, sir.

Mr. GORE. That was the single dissenting opinion.

Dr. TODHUNTER. I so indicated.

Mr. GORE. OK.

Dr. TODHUNTER. We must not forget that the CPSC originally became interested in control of urea formaldehyde insulation before CPSC was aware that formaldehyde might have carcinogenic potential. CPSC's concerns were with a variety of health effects, and Dr. Preuss, who preceded me, has testified to that effect.

Statutorily, EPA's consideration under section 4-f of TSCA deals only with significant risk from cancer, gene mutation, or birth defects. Of all the exposure situations looked at by the Office of Toxic Substances, OTS, more than 97 percent of exposed individuals under our jurisdiction are exposed levels lower than the 0.1 ppm discussed by Commissioner Statler. A fraction of a percent might be exposed to higher levels but OTS documents have always expressed considerable uncertainty as to whether such higher exposure estimates are reliable. That is why OTS has believed all along that an exposure assessment program for selected exposures is the correct first approach.

Neither has there been any evidence of great concern in the scientific community over OTS staff work or my subsequent concurrence with OTS's recommendation. We have received no complaints from the scientific community. We have received fewer than a dozen adverse comments from anyone on the February 10 memorandum. Indeed, I would like, with your permission, to introduce into the record letters or memoranda from Dr. John Higginson, the former Director of the International Agency for Cancer Research; Dr. Steven Sternberg, who is with the Sloan Kettering Memorial Cancer Center; Dr. James Gibson, vice president and director of research, and Dr. James Swenburg, chief pathologist, for the Chemical Industry Institute of Toxicology, and Dr. Roger Maickel, head of the Department of Pharmacology and Toxicology at the Purdue University School of Pharmacy and Pharmacal Sciences, which indicate their agreement that EPA's science in the matter is sound.

We have heard from a panel this morning which has made statements as to what is science policy, in this area. I would like to read some other statements into the record which indicate that the panel's picture of general unanimity on these issues is far from correct. I will read to you:

> Although the production of neoplasia in animals at a statistically higher level than in controls has been considered indicative of carcinogenicity of the agent under study, modern concepts of the natural history of neoplastic development require that this simplistic reevaluation of the data be considered.

Now this is not from some radical scientist. This is written in the second edition of a standard textbook in oncology by Dr. Henry Pitot, who from 1979 to 1982 was chairman of the National Cancer Advisory Board. Dr. Pitot writes further——

Mr. **Gore**. Where are you reading from, Dr. Todhunter?

Dr. **Todhunter**. This is from "Fundamentals of Oncology." I will submit this for the record if you so wish.

Mr. **Gore**. OK. This is not a statement, is it?

Dr. **Todhunter**. No, sir.

Mr. **Gore**. Go ahead.

Dr. **Todhunter** [reading]:

> At very low doses of a chemical, the time until the appearance of a neoplasm may be extended to such a length that it exceeds the lifetime of the test animal. Thus, although most investigators today would not argue strongly against a dose response relation for chemical carcinogens, there is increasing question of the hypothesized no-threshold level of effect for chemical carcinogens as a practical consideration.

Again from Dr. Pitot's standard textbook in oncology.

The question of cytotoxicity has been discussed earlier today, and I read to you from the report of the Federal Formaldehyde Panel chaired by Dr. Griesemer: "In short, it is conceivable that the cytotoxic effects of formaldehyde may play a part in its overall carcinogenicity."

Now what does the American Medical Association have to say about this subject?

Mr. **Gore**. Excuse me. Were you just quoting from Dr. Griesemer?

Dr. **Todhunter**. No, sir. This is from the Federal Report on Formaldehyde which Dr. Griesemer chaired.

Mr. **Gore**. Which Dr. Griesemer chaired?

**Dr. TODHUNTER.** Yes, sir.

**Mr. GORE.** Well, we had him here this morning.

**Dr. TODHUNTER.** Well, we did not hear that exact statement from him. This morning there seemed to be disagreement as to whether cytotoxicity was involved.

The special study group of the American Medical Association on July 17 published in the Journal of the American Medical Association a report——

**Mr. GORE.** Dr. Todhunter, none of this is in your prepared statement and you are taking selected quotations from a series of documents that you have not given us a chance to review or look at. I mean, to quote Dr. Griesemer's work is——

**Dr. TODHUNTER.** Sir, these are documents which should be familar to anyone——

**Mr. GORE.** Excuse me. Let me finish, please. To cite work by Dr. Griesemer as supporting your scientific analysis, I think illustrates the problem that we have in taking selected quotations from documents that we do not have a chance to review or look at. They are not appended to your statement. We have no way to evaluate them. I mean, you know, Dr. Griesemer——

**Dr. TODHUNTER.** Are you saying you would dispute that Dr. Griesemer has included this in a report from a panel which he chaired? This has, in fact, been a public document for quite some time.

**Mr. GORE.** I do not question that. I question its relevance when it is a selected quotation out of——

**Dr. TODHUNTER.** Sir, the panel that was here this morning was a selected panel.

**Mr. GORE.** Excuse me, Dr. Todhunter, please. I will give you a chance to respond.

**Dr. TODHUNTER.** Thank you.

**Mr. GORE.** The problem that we have is that in taking it out of its context without any ability for us to review other parts of the document. That is the only problem. I mean, if you want to read selected quotations from documents that we have not seen, out of courtesy I will afford you the opportunity to do that but it is just of limited usefulness or relevance.

**Dr. TODHUNTER.** Well, I contend that——

**Mr. WALKER.** Mr. Chairman, if you would yield——

**Mr. GORE.** Yes, I would be very glad to yield.

**Mr. WALKER.** I think that we got some very selective information from the panelists that we had this morning, as well, so——

**Mr. GORE.** However, all of their testimony was made available to us and we had a chance to review it. It was made available to the minority who had a chance to question it, and it was made available to EPA as well. None of this is appended to his testimony. It has not been available. We have no way to analyze it.

**Mr. WALKER.** If the chairman would yield——

**Mr. GORE.** I would be glad to yield.

**Mr. WALKER** [continuing]. I understand from Dr. Todhunter that this particular document from which he has quoted has been available for some time as a public document. It seems to me that probably we should be familiar with that, plus the fact that we requested much information from EPA which they provided to us, which I have to say was not provided to the minority in time for us to review it.

Mr. Gore. Well, there is just nothing that we got from EPA that has not been made available to the minority.

Mr. Walker. We did not receive it in a timely fashion, Mr. Chairman.

Mr. Gore. Neither did we. [Laughter.]

Mr. Walker. Well, as I understand it, Mr. Chairman, you requested on a Friday that they have it up here on a Monday and that was when it was delivered. At the point of yesterday, we still had not seen most of those documents.

Mr. Gore. All right. We will revisit that on another occasion.

Dr. Todhunter, are you through with your statement?

Dr. Todhunter. No, sir, I am not quite finished.

Mr. Gore. Are you through with your prepared statement? You have some other stuff you want to read?

Dr. Todhunter. In fact, no, I have more to say on the prepared statement to the tune of a paragraph. If the Chair will indulge me——

Mr. Gore. Sure.

Dr. Todhunter [continuing]. To enter these statements, I feel that they are appropriate, as they do address points raised in the question and answer following the prepared testimony of the earlier panel, and these are things which certainly we could not anticipate and which I felt needed to be addressed.

The impression was given by the earlier panel that there is no dissension within the scientific community, as these are the established, orthodox principles. These principles actually were enumerated some 10 years ago and have subsequently undergone quite a lot of discussion. I think it is important for the subcommittee to be aware of that as well.

Anyway, the American Medical Association has stated, in a report adopted by their house of delegates, that:

> Carcinogenicity in animal tests does not per se predict either risk or outcome in the human experience. Moreover, an agent can metabolize differently in diverse species and even strains of mice. Thus, a substance can be carcinogenic for certain organs in one species but relatively harmless in other organs or in other species.

Furthermore, in the same report AMA states:

> There is some evidence from both experimental animals and man that there is a threshold for many carcinogens. Thus the concept of a threshold level beneath which exposure is harmless cannot be rejected.

I just add that to indicate that I do not think it is by far unanimous that there is only one way to look at tumor data.

Mr. Chairman, I trust that I have been able to clear up the misconceptions regarding TSCA section 4-f and EPA's actions concerning formaldehyde. EPA believes that the approach which is being taken is reasonable, proper, and prudent.

This concludes my statement and I will be more than happy to answer any questions which the subcommittee may have.

[The prepared statement of Dr. Todhunter follows:]

# STATEMENT OF
# JOHN A. TODHUNTER, Ph.D.
ASSISTANT ADMINISTRATOR FOR
PESTICIDES AND TOXIC SUBSTANCES
ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT
COMMITTEE ON SCIENCE AND TECHNOLOGY
HOUSE OF REPRESENTATIVES

MAY 20, 1982

Mr. Chairman, members of the Subcommittee, good morning. I welcome the opportunity to be here this morning to discuss with you the status of the EPA's program on formaldehyde. The interest of the Subcommittee is understandable given the numerous misconceptions and misrepresentations about our approach to formaldehyde which exist. I believe firmly that once I have identified the nature of these misconceptions, the members of the Sucbommittee will understand that EPA's actions have been scientifically defensible and true to the intent of the Toxic Substances Control Act (TSCA).

I should like to address each of these misconceptions:

Misconception #1: The previous administration was proposing to regulate formaldehyde.

Fact - At no time in the past did EPA propose to regulate formaldehyde. The previous administration proposed only to conduct a two year exposure analysis and risk assessment program. This program was to have started in 1981 and to have ended around October of 1983.

In fact, this program, in a stronger and more expedited form I might add, is presently being initiated by EPA. We are moving to establish several expert review panels to consider specific formaldehyde issues. These panels will be run under the auspices of the National Center for Toxilogical Research and will tap the scientific expertise of government agencies, academia, and industry. We hope to hold a consensus building workshop within a year and will be able to significantly improve the quality of our exposure and toxicological data well ahead of the previously proposed schedule.

The difference in our approach, concerns the use of section 4(f) of TSCA. Section 4(f) itself is not a "regulatory vehicle," but rather a priority setting mechanism. This section was placed in the law to ensure that significant health risks from cancer, gene mutations and birth defects receive priority action. This section of TSCA requires the exercise of judgement and is, therefore, a discretionary action on the part of the Administrator.

Section 4(f) does require the Administrator to initiate rulemaking action within 180 days under sections 5, 6, or 7 of TSCA, when the Administrator receives information that leads her to conclude - on a reasonable basis - that a significant risk of serious or widespread harm from only cancer, gene mutations or birth defects is presented or will be presented by a chemical substance. The statute does not authorize use of section 4(f) for any risk.

The statute also doesn't say "if it's 4(f) go out and spend two years investigating." It says "go out and regulate" unless you can make a finding within 180 days that the "significant" risk is not unreasonable. Regulations shall be under section 5, new chemical substances; section 6, hazardous chemical substances; or section 7, imminent hazards. It takes at least six months to develop a clear defensible regulatory proposal. That means you must have a substantial amount of the data in hand before you invoke section 4(f). This is a very important point. The concept of using an exposure investigation as a response to a section 4(f) finding is contrary to the statute. Any documents which make such a recommendation are, then, irrelevant as they propose actions contrary to law. Such recommendations must - the science aside - be dismissed out of hand.

In summary, the question the Agency faced was straight forward: is the available evidence sufficient to point EPA toward expedited rulemaking or not?

The answer to this question has always been no. That is why EPA in the past had proposed an exposure "investigation" to be done over two years. The Agency very much needed reliable data on specific exposure situations then; it very much needs it now. That is why, as I have mentioned previously, we have refined the investigatory proposal, are carrying it out, and expect to bring in the necessary information a half year ahead of what the previous administration hoped to be able to do.

A listing of formaldehyde as a section 4(f) chemical is at present inappropriate. You don't call something a "significant" risk and then say "we need to get exposure data". The proper scientific approach would be to say "we need exposure data", then to go out and get that data, and only then make an intelligent, factually based decision concerning the use of section 4(f) or any other section of TSCA. That is what this administration is doing.

Misconception #2: EPA has "departed" from long standing principles of risk assessment in developing its position on formaldehyde.

Fact - EPA considers formaldehyde to be a carcinogen in the rat by the inhalation route and probably also in the mouse by the same route. EPA presumes - as do I personnally and professionally - that formaldehyde may, in theory, pose a risk of cancer to humans. EPA also holds that animal testing, carefully analyzed, is an appropriate indicator of potential human risk.

Whether or not a substance may pose any risk of cancer to humans, however, is not the issue under TSCA section 4(f).

The issue is whether or not the cancer risk is "significant". The question is, simply put: "Is this a high degree of risk or a low degree of risk?" The answer to that question depends intimately on exposure. The exposure information presently available to OTS indicates that carcinogenic risk for most, if not all, uses of formaldehyde is in a range that regulatory agencies normally consider low. Indeed, the existing exposures are in the range that regulatory agencies often seek to achieve when they do impose controls. At these low risk ranges one would not expect to actually find any detectable excess of tumors in the population at risk.

Allow me to quote from the dissenting opinion on the urea formaldehyde insulation ban of Consumer Product Safety Commissioner Stuart M. Statler:

> "...CPSC staff confirm that formaldehyde is regarded as a relatively weak carcinogen. Hence, the probable cancer risk associated with exposure to formaldehyde gas appears considerably less serious than the risks from other known cancer causing agents. By way of comparison, the very same Canadian government which barred urea formaldehyde foam identifies the added cancer risk associated with 0.1 ppm formaldehyde exposure comparable to smoking only one-third of a cigarette daily."

We must not forget that CPSC originally became interested in control of urea formaldehyde insulation before CPSC was aware that formaldehyde might have carcinogenic potential.

CPSC's concerns were with a variety of health effects. Statutorily, EPA's consideration under section 4(f) of TSCA deals only with significant risks from cancer, gene mutations, or birth defects.

Of all the exposure situations looked at by the Office of Toxic Substances (OTS), more than 97% of exposed individuals are exposed to levels lower than the 0.1 ppm discussed by Commissioner Statler. A fraction of a percent might be exposed to much higher levels but OTS documents have always expressed considerable uncertainty as to whether such higher exposure estimates are reliable.

That is why OTS has believed all along that an exposure assessment program for selected exposures is the correct first approach.

There has not been "great concern in the scientific community" over OTS staff work or my subsequent concurrence with OTS' recommendation. We have received no complaints from the scientific community. We have received fewer than a dozen adverse comments from anyone on the February 10 memorandum. Indeed, I would like, with your permission, to introduce into the record letters or memoranda from Dr. John Higginson, former Director of the International Agency for Cancer Research; Dr. Steven Sternberg, Sloan Kettering Memorial Cancer Center; Dr. James Gibson, Vice President and Director of Research and Dr. James Swenburg

Chief Pathologist for the Chemical Industry Institute of Toxicology; and Dr. Roger Maickel, Head, Department of Pharmacology and Toxicology, Purdue University School of Pharmacy and Pharmacal Sciences, which indicate their agreement that EPA's science in this matter is sound.

Mr. Chairman, I trust that I have been able to clear up the misconceptions regarding TSCA section 4(f) and EPA's actions concerning formaldehyde. EPA believes the approach being taken is reasonable, proper, and prudent. This concludes my prepared statement. I will be happy to answer any questions which the Subcommittee may have.

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February 12, 1982

The Honorable Nancy Harvey Steorts
Chairman
Consumer Product Safety Commission
1111 18th Street, N.W.
Washington, D.C. 20036

Dear Madam Chairman:

As former director of the International Agency for Research on Cancer (IARC), Lyon, France, I wish to comment on certain issues arising out of the recent reports from the Consumer Product Safety Commission and the press. My comments relate first to the interpretation of the Agency's evaluation and the second to certain generic issues.

The evaluation of formaldehyde was part of a systematic, long-term program by the agency on the evaluation of carcinogenic risks of chemicals to humans. These evaluations are compiled by groups of experts who act as advisors to the director and are selected by the agency's secretariat. The report represents the opinion of the working party and is not an official position by the IARC. If he considers it desirable, the director may require further consideration of an evaluation by another working party. When I left the agency, the second report on formaldehyde was still in draft form and I presume the comments in the press were based on the latter, even though it had not been published or finalized. However, there would appear to be no doubt that formaldehyde causes cancer in one species of rodents and this part is not disputed. Clarification is, however, necessary regarding the interpretation of the group's evaluation.

Based on the analysis of available material the group uses for its summary evaluation a formular wording which includes the phrase "for practical purposes."
This evaluation must be read in the context of the preamble of the monographs which includes a number of caveats as to the limitation of the evaluation. When the present terminology was adopted some years ago, it was assumed that it would be interpreted scientifically by national bodies giving full consideration to the caveats and not as a regulatory recommendation. In the present case, this does not seem to have been fully appreciated. The preamble states: "For many of the chemicals....for which there is sufficient evidence of carcinogenicity in animals, data relating to the carcinogenicity in humans are either insufficient or non-existent. In the

absence of adequate data on humans, it is reasonable, for practical purposes, to regard such chemicals as if they present a carcinogenic risk to humans." However, it is quite clear from the context that this was not to be interpreted without further qualifications to mean that a compound carcinogenic to animals. was to be considered a human carcinogen. In practice, the risk to humans could range from practically zero to being very considerable and the same phraseology could be used in the evaluation.

The complexities of extrapolation of potency from animals to man are briefly described in the preamble and no working party during my directorship ever stated that such an extrapolation could be made with any degree of credibility. In fact, the first sentence in the preamble states, "No adequate criteria are presently available to interpret experimental carcinogenicity data directly in terms of carcinogenic potential for humans." Possible methods of doing so are discussed in the preamble but, to date, I am unaware that any acceptable scientific method has as yet been developed for any known chemical carcinogen. Today few experienced experimental oncologists would make any attempt to extrapolate mathematically the degree of human risk from animals, although such attempts were fashionable among biostatisticians in the early '70's when the complexities inherent in modern theories of carcinogenesis in man were not appreciated. Exact estimates as to the number of cases of a cancer that might be expected to occur in man based on a single experiment are lly and simply ignore biological realities. The fact that no better methods exist does not make these estimates any better or more valuable. Thus, in the absence of human material, at no time has the agency or its workshops ever attempted to define "safety" which is in fact a mathematical probability.

The second point relates to the question of human data. In the past, the agency's monographs have tended only to discuss specific published analytical studies and avoided evaluation of circumstantial epidemiological and biological data. The latter may be considerable but requires a large degree of biological knowledge, intelligence and flexibility by very experienced epidemiologists for interpretation. Many epidemiologists, however, believe that such data should at least be taken into consideration by national bodies when making an overall evaluation as to policy. The use of such data has played a role in evaluating saccharine and DDT. Accordingly, where an evaluation of formaldehyde has been attempted, as here, it would appear advisable to give consideration to human data from other sources.

In this case, the type of cancer one might believe to be produced by formaldehyde gas is normally rare. Any marked excess should be easy to recognize in view of the large scale on which the chemical has been used for many years. Whereas proportional mortality rates from cancer are poor in terms of positive evidence of an occupational risk, because an increased proportion of a cancer may occur as a result of reduced mortality from other causes due sometimes to the "healthy worker effect", they may provide excellent evidence as to the absence of a risk if the proportion of death due to a particular type of cancer is low. It should also be pointed out that in the wood industry there have been extensive studies regarding an increase in the risk of nasal cancer in this occupation. However, the data suggests that the increase is most likely to occur among carpenters and may be associated with certain hardwoods. It has not been reported in those portions of the wood industry where rmaldehyde is most likely in general use. The extensive studies on occupa-ional mortality in the United Kingdom, to which no reference is made in your report, only show an increase in nasal cancer in butchers and no mention is made of an increase in other occupations. It is interesting, moreover, that studies on pathologists in the United Kingdom by Doll and Peto and elsewhere also show no increase in nasal or other cancers that could be attributed to formaldehyde yet pathologists in the past were exposed extensively. All studies quoted are typical of a negative situation.

In nearly all countries, irrespective of their degree of industrial development, the incidence of nasal cancer is surprisingly constant and in a number of developed countries where formaldehyde has been widely used, the risk of nasal cancer is in fact falling. All these data taken together are insufficient to completely exclude a minimal risk, but certainly they weigh heavily against the view that formaldehyde gas constitutes any considerable risk for nasal cancer to man.

I believe that the circumstantial data above is important and raises a significant generic issue as to the value and strength of negative data. Anyway, it is my opinion that all available human observations should be used by the commissioners in evaluating the carcinogenicity of the gas.

None of the above comments should be interpreted as implying that careless se of formaldehyde compounds is desirable or that formaldehyde does not have leasant side effects at certain levels of exposure especially among sensi-ve individuals.

Sincerely yours,

John Higginson, M.D.
Senior Executive Scientist

JH:dr
cc: The Honorable R. David Pittle
The Honorable Samuel Zagoria
The Honorable Stuart Statler
The Honorable Edith Barksdale Sloan

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

May 14, 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM FOR THE RECORD

SUBJECT: Telephone Conversation with Dr. Stephen Sternberg Returning Comments on the February 10 Concurrence Memo of Dr. Todhunter

Dr. Sternberg called on May 14 to deliver comments on the February 10 memo. He said that he would follow up with a note.

Dr. Sternberg found the February 10 memo "very good" and "very clear". He "hasn't seen very many analysis of this high quality".

He had no criticisms to make.

Dr. Sternberg requested some information regarding the degree of metastases in the CIIT study which I promised to ask to have sent to him.

John A Todhunter

John A. Todhunter, Ph.D.
Assistant Administrator
for Pesticides
and Toxic Substances

cc: Dr. Sternberg

## MEMORANDUM TO THE RECORD

SUBJECT: Telephone conversation of May 12 with Dr. James Gibson of CIIT regarding the February 10 concurrence memo on formaldehyde of Dr. John A. Todhunter

Background:

CIIT was sent a copy of the Feb. 10 concurrence memo for formal comment. By telephone conversation on May 12 Dr. Gibson of CIIT returned both his and Dr. Swenberg's comments. Dr. Gibson is Vice President and Director of Research at CIIT. Dr. Swenberg had charge of CIIT's formaldehyde bioassay program.

Notes on conversation:

Dr. Gibson stated that he was transmitting his and Dr. Swenberg's comments on the Feb. 10 memo. He had some general comments:

- CIIT has "no problems" with the analysis presented in the Feb. 10 memo regarding formaldehyde carcinogenicity.
- He doesn't see anything radical in the Feb. 10 analysis.
- The Feb. 10 memo "told it like it is".

Dr. Gibson also had a few, minor specific comments:

- Newer CIIT measurements of endogenous formaldehyde levels give a range (depending on tissue) of 1.5 ng/g to 15 ng/g or 1.5 ppm to 15 ppm formaldehyde (the Feb. 10 memo, relying on preliminary CIIT data had endogenous levels of 3 ppm - 12 ppm).
- They agree that 10% - 40% (as stated in the Feb. 10 memo) is reasonable for non-glutathione bound formaldehyde. The current CIIT estimate of 2% or less "free" formaldehyde refers to forms not as glutathione or tetrahydrofolate adducts (the Feb. 10 memo used "free" in reference to non-glutathione bound formaldehyde). Discussion revealed that CIIT agrees that - as a fundamental principle of biochemistry - it is academic just what proportion of formaldehyde is bound to glutathione and tetrahydrofolate as this is an equilibrium system and all of the endogenous formaldehyde should be available to react with the genome via equilibrium displacement. Any arguments that endogenous formaldehyde isn't

available to the genome since little is "free" are ignoring the fundamental principle of dynamic equilibrium.

- The explanatory comment on page 8 that animals developed open sores after which tumors appeared is oversimplified for the lay reader. Gibson notes that the ulceration seen after exposure eventually healed (after adaptive mechanisms took over) but the squamous metaplasia and epithelial dysplasia remained during the course of treatment.
- The squamous metaplasis (footnote) at 2 ppm was completely reversible even after 24 months exposure to formaldehyde (confirmed by examination at 27 months) and the epithelial dysplasia at 2 ppm (see footnote) was 50% reversible under the same conditions. At 6 ppm and 15 ppm there was also reversability but not to the intent seen following the 2 ppm treatment. (The Feb. 10 memo referred to reversal of formaldehyde induced hyperplastic and metaplastic effects at low levels of exposure following cessation of exposure but did not give a quantitative aspect to this phenomenon.)

John A Todhunter 5/12/82

John A. Todhunter, Ph.D.
Assistant Administrator
for Pesticides
and Toxic Substances

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footnote:

Metaplasia is the conversion of one kind of tissue into a form not normal for that tissue. Dysplasia refers to any abnormal development of tissue [Taber's Cyclopaedic Medical Dictionary]. As used by pathologists, dysplasia refers primarily to the alteration of the arrangement and size of cells, it is not the same as anaplasia which is characterized "by alterations in intracellular macromolecular synthesis and intercellular relations and associations" [Pitot, Fundamentals of Oncology, Dekker, N.Y. (1981)].

cc: Dr. James Gibson
Dr. Swenberg

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

May 14, 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM FOR THE RECORD

SUBJECT: Telephone Comments of Dr. Roger Maickel on the February 10 Concurrence Memo of Dr. Todhunter

Dr. Maickel called on May 14. He and Dr. Gary Carlson (a professor of toxicology at Purdue) had reviewed the February 10 memo. They have no major problems with any of it but have some minor questions on points where the memo is a bit terse. These are not criticisms per se. The science is accurate. The analysis would benefit if it were less terse on some points. I replied that I agreed with this comment since the science underlying some points was purposely kept terse as the document was intended for a reader that was not scientifically oriented. I noted that I was in the process of updating the memo to expand on some of these same points.

Dr. Maickel said that he would follow-up with a letter.

John A Todhunter

John A. Todhunter, Ph.D.
Assistant Administrator
for Pesticides
and Toxic Substances

cc: Dr. Maickel

Mr. **Gore**. Thank you very much, Dr. Todhunter.

Now during the time that you were making this decision—well, first of all what is the EPA decision document on formaldehyde?

Dr. **Todhunter**. I am not sure if you are referring to the memorandum of Mr. Clay from September 11, which in fact was the point at which the recommendation was made, or if you are referring to any of the technical support documents, or if you are referring to the update memorandum and concurrence which I prepared for the Administrator on February 10.

Mr. **Gore**. Well, I am asking you: Which is the decision document?

Dr. **Todhunter**. Basically it would be the memorandum of September 11 from Mr. Clay to the Administrator.

Mr. **Gore**. Now there has been nothing in the Federal Register. Is that correct?

Dr. **Todhunter**. There has been nothing in the Federal Register for the simple reason that section 4-f is not a regulatory activity. We have never to date had the opportunity to invoke section 4-f but it would not be our opinion that we would need to publish a finding one way or the other in the Federal Register.

Mr. **Gore**. Well, Dr. Hernandez, the Deputy Administrator, wrote after the Clay memorandum, he wrote on October 5, "I have not yet fully completed my scientific and technical analysis of the available data with respect to either substance, and my decisionmaking process on these issues is not yet complete." Therefore, a month or almost a month after the document that you say is the decision document, the Deputy Administrator is saying there has been no decision.

Dr. **Todhunter**. The Deputy Administrator would not have the final responsibility for that decision and I cannot speak for his mind because once things go up to the 12th floor, we do not know how long it takes them to decide. The September 11 recommendation that came out of OTS is the one which we would stand by.

Mr. **Gore**. Now in March of this year, on March 4, the Deputy Administrator, Dr. Hernandez, wrote to Dr. Keyworth and referred to the recent decision: "* * * as recently released, the analysis used in reaching a decision on formaldehyde's possible classification as a priority chemical." Indeed, 2 days after your memo was dated there was a public release from EPA, "Environmental News," a press advisory: "This notice is to make available to all interested parties a paper prepared by Dr. John A. Todhunter, Assistant Administrator for Pesticides and Toxic Substances," and it talks about formaldehyde.

Then, as I say, after that Dr. Hernandez writes to the Science Advisor to the President and says, "EPA has recently released the analysis it used in reaching a decision on formaldehyde's possible classification as a priority chemical." Now a reasonable person would conclude from that sequence of events that the decision document is your memo.

Dr. **Todhunter**. It is entirely possible that the Deputy Administrator has overstated the importance of my memo. I cannot speak to his frame of mind. In fact, the notice of availability states that "the document concurs with the current recommendations of the Office of Toxic Substances," so it quite clearly indicates in that release that there was concurring with a current recommendation——

Mr. GORE. Which you endorsed in your memo.

Dr. TODHUNTER. Which I endorsed.

Mr. GORE. However, you did not endorse the science.

Dr. TODHUNTER. I endorsed the current recommendation which rested on the science. I do not see how you can make the two distinct.

Mr. GORE. Then why is the science different?

Dr. TODHUNTER. The science is the same.

Mr. GORE. The science not the same. We will get into that in some detail. However, the memo itself, dated February 10, is from you through John Hernandez to Anne Gorsuch. The point is—and it may seem like an arcane point—the point is that the evidence clearly indicates that the decision document in this matter is the February 10 memorandum prepared by you.

Dr. TODHUNTER. No, sir. In fact, the problem that we were faced with was that back in September, the staff had pretty clearly concluded that what they needed to do was to get exposure data and that that certainly was not the way to go at a 4-f. At that point we were being threatened with a lawsuit from NRDC and Mr. Clay prepared a memorandum simply to put us on record as saying that we in fact did not think 4-f was applicable here, and therefore, why are you talking to us about a lawsuit?

That memorandum was picked up in the trade press and generally reported that EPA has decided it is not going to put things under 4-f. Subsequently, we still received a lot of intimations from NRDC that we might be sued and we——

Mr. GORE. This was on February 10?

Dr. TODHUNTER. This was on into January and February, and subsequently we decided that we simply needed to restate the matter for the record.

Mr. GORE. Now what role did you play in revising the PRL-1?

Dr. TODHUNTER. Quite frankly, a very limited role. The staff asked me for comments on some of the molecular biological aspects of the document, since that is where my particular expertise lies, I provided some. The staff decided that they really were making an exposure-based argument more so than one based on the molecular biology of the process, and therefore the staff decided that my comments, which I provided on a purely voluntary basis, would not appear in the technical document as it might complicate the argument on exposure.

Mr. GORE. On what basis did you participate in this revision?

Dr. TODHUNTER. Simply to provide some comments on a portion of the document having to do with the molecular biology involved.

Mr. GORE. What role did you play in revising the technical documents?

Dr. TODHUNTER. That is what I was just referring to.

Mr. GORE. They are different documents.

Dr. TODHUNTER. The technical document is what you are talking about.

Mr. GORE. I was referring, first, to the PRL-1.

Dr. TODHUNTER. Oh, I am sorry. I misheard you. The PRL-1 I had no role in.

Mr. GORE. You had no role at all in revising the PRL-1?

Dr. TODHUNTER. No, sir. The technical document was——

Mr. GORE. You provided comments to the PRL-1.

Dr. TODHUNTER. I provided comments at the time that the technical document was being prepared from the PRL-1 as a basis. The PRL-1 evolved into the technical document by some mechanism.

Mr. GORE. You also made substantial comments on the various revisions to the technical documents.

Dr. TODHUNTER. I made substantial comments to one revision of the technical documents. The staff indicated back to me that, thank you, but we really were more interested in making an exposure case and therefore I said, "Fine, I am not going to make any more comments."

Mr. GORE. What was the source of the information provided in your comments?

Dr. TODHUNTER. A variety of references, also personal communication with Dr. Hech and Dr. Swenburg at CIIT.

Mr. GORE. Any other communications?

Dr. TODHUNTER. No, sir.

Mr. GORE. Anything from the Formaldehyde Institute?

Dr. TODHUNTER. Nothing that I can specifically think of, no.

Mr. GORE. Did you have meetings with the Formaldehyde Institute folks during this time?

Dr. TODHUNTER. I attended two. At Dr. Hernandez' request, I attended two of the briefings that were put on by OTS for Dr. Hernandez, at which the Formaldehyde Institute participated and at which other people were present.

Mr. GORE. What about other meetings with representatives of the Formaldehyde Institute? Any others that you can remember?

Dr. TODHUNTER. No, sir.

Mr. GORE. What about breakfast meetings with people at the Formaldehyde Institute?

Dr. TODHUNTER. Not prior to the February 10 memorandum.

Mr. GORE. What about John Byington?

Dr. TODHUNTER. After the February 10 memorandum.

Mr. GORE. I do not want to play cat-and-mouse with you. Let me just tell you that our records indicate that you had a breakfast meeting with John Byington, the lawyer, the "strategic counsel" as he says of the Formaldehyde Institute, on January 15.

Dr. TODHUNTER. That is quite incorrect, sir. Your records will indicate or should indicate that that was a snow day. I was scheduled to have a breakfast with Mr. Byington and some other people not associated with the Formaldehyde Institute but I never showed up.

Mr. GORE. What about January 26?

Dr. TODHUNTER. I did not show up to a breakfast that I was to have with Mr. Byron Nelson, who subsequently informed me that he had suggested to Mr. Byington that Mr. Byington might want to join the breakfast party.

Mr. GORE. Therefore, both of these breakfast meetings are on your calendar but you are saying that neither one took place?

Dr. TODHUNTER. That is correct.

Mr. GORE. What about telephone conversations with Mr. Byington?

Dr. TODHUNTER. That is difficult to say.

**Mr. Gore.** Why?

**Dr. Todhunter.** Because I do not remember specifically when I may have called Mr. Byington or when I may have not. I do not keep a telephone log or anything like that.

**Mr. Gore.** Did you have breakfast with Mr. Byington—let's go back to January 26. You are saying that you did not show up for that?

**Dr. Todhunter.** No, sir. I overslept. 1 got to the breakfast point with Mr. Nelson and the party was breaking up. I said hello, grabbed a cup of coffee for myself, and everybody went their way.

**Mr. Gore.** Now, wait a minute. Wait a minute. Were you there or were you not there?

**Dr. Todhunter.** I was not there for breakfast. As I said, I was going to have breakfast with Mr. Nelson——

**Mr. Gore.** Oh, you see, I got the impression earlier that you were not there.

**Dr. Todhunter.** No, I was not. I overslept the breakfast. I got there and because it happened to be on the way to work, I dropped in to say hello and apologize for missing breakfast, and I did that and then I left.

**Mr. Gore.** Well, I am glad I came back to it because I got the erroneous impression earlier that you did not meet with Mr. Byington on January 26. Maybe that is just the fact that I did not listen carefully to what you said, Dr. Todhunter. In fact, you did meet with him on January 26, right?

**Dr. Todhunter.** I said goodbye to him in passing. I did not have a chance——

**Mr. Gore.** Did you say hello before you said goodbye?

**Dr. Todhunter.** Yes. I said, "Hello. Sorry I am late. I have to run."

**Mr. Gore.** OK. Now you and Mr. Byington were together members of the American Council on Science and Health. Is that correct?

**Dr. Todhunter.** Not exactly. I was a scientific adviser for the Council and Mr. Byington was a policy adviser. Mr. Byington is a lawyer by training. He has degrees in pharmacology and was not a member of the scientific advisory board but we were both associated with the Council.

**Mr. Gore.** I see. The two, you and Mr. Byington, were both associated with the American Council on Science and Health at the same time, correct?

**Dr. Todhunter.** That is correct.

**Mr. Gore.** That is an industry-funded group.

**Dr. Todhunter.** No, it is not.

**Mr. Gore.** It is not?

**Dr. Todhunter.** No, sir. It derives its funding from a variety of sources. Some of them are industrial foundations. As of about a year or a year and a half ago, ACSH did change their bylaws to allow some input of direct funding from corporations that were involved in food and drugs.

**Mr. Gore.** Well, maybe we can supplement the record on that point.

Now at another subcommittee when you were asked about your meeting with the lawyer for the industry prior to this memorandum, you were asked about this January 26 meeting and you were asked if you had breakfast at the Holiday Inn on January 26. Your answer was, "I think I did in fact have breakfast with him but at a different location."

However, you are saying that you did not discuss formaldehyde, however, long your contact with Mr. Byington at that time.

Dr. TODHUNTER. Oh, yes, certainly, sir.

Mr. GORE. You are saying you did not discuss formaldehyde?

Dr. TODHUNTER. No.

Mr. GORE. However, you are not sure whether you discussed it with him on the telephone prior to that time?

Mr. TODHUNTER. My recollection is that I probably obtained from Mr. Byington a telephone number for Dr. Hech at CIIT when I wished to communicate with Dr. Hech. To my recollection, that may be the extent and I believe it is the extent of my telephone contact with Mr. Byington on formaldehyde prior to February 10.

Mr. GORE. Now during that conversation, did you discuss formaldehyde with Mr. Byington?

Dr. TODHUNTER. I do not recall the substance of the conversation. I called up his office and asked if anybody could supply me with the number of Dr. Hech. They put on Mr. Byington, I believe, and I asked, "Do you have the number for Dr. Hech at CIIT?" He provided me with the number and I said, "Thank you," and we did not discuss the subject of formaldehyde.

Mr. GORE. Well, OK.

Now the director of your Office of Toxic Substances, Mr. Clay, you used to work for Mr. Byington, did you not?

Mr. CLAY. I was at the Commission at the same time Mr. Byington was the chairman, yes, sir.

Mr. GORE. What position did you hold?

Mr. CLAY. I held three positions at CPSC: overall planning, budgeting, and evaluation; then acting head of engineering and sciences; and then head of engineering and sciences. With Mr. Byington I was transitioning from one to the other, so I was originally head of planning, budgeting, and evaluation, and then became the acting head for engineering and sciences.

Mr. GORE. Now, Dr. Todhunter, did you review your memorandum with CPSC prior to sending it on to the Administrator?

Dr. TODHUNTER. No, sir; I did not.

Mr. GORE. Did you know that the CPSC decision was to be made in February?

Dr. TODHUNTER. It was to be made at some point but CPSC was already quite familiar with our position on the subject of section 4f and I saw no further need to pass additional material——

Mr. GORE. I am talking about the science issue, not the regulatory decision.

Dr. TODHUNTER. On the science issue, CPSC should have already been aware because it was basically that which was represented in our technical document. There was no new science issue to present.

Mr. GORE. Well, we will get into that.

Who on your staff reviewed your memo before you sent it to the Administrator?

Dr. TODHUNTER. I asked Dr. Hill, who is one of my science advisors, to take a quick look at it. I am not sure if he had a chance to do so. It was sent up through Dr. Hernandez because Dr. Hernandez was supposed to arrange for some type of review of the document.

Mr. GORE. Now, wait a second. Dr. Hill told the staff that he did not.

Dr. TODHUNTER. OK. I said I do not know if he had time to look at it. I asked him to have a quick look at it and I just said that I am not sure he had the time to look at it because he was busy with other things. The review of the document normally should have occurred at a level higher than myself. It should have occurred at the level of Dr. Hernandez because we normally do not review documents at our own level.

Mr. GORE. Dr. Hill said he saw it going to the Administrator, did not have a chance to review it.

Dr. TODHUNTER. OK.

Mr. GORE. Who did review it on your staff?

Dr. TODHUNTER. I haven't the slightest idea. Nobody on my staff personally reviewed it, no.

Mr. GORE. Nobody on your staff?

Dr. TODHUNTER. It would not be the usual thing to do.

Mr. GORE. It would not be the usual thing to review a scientific document of that kind?

Dr. TODHUNTER. No. It was drawn generally from the data in the PRL-1 and in the technical document which had already been looked over quite a bit. I saw no need, since this was simply a compilation and summary and update, no need for a further round of review at that level.

Mr. GORE. Well, PRL-1 recommended action on formaldehyde, didn't it?

Dr. TODHUNTER. PRL-1 recommended that we needed to do an exposure analysis and that section 4-f might be the way to go for it.

Mr. GORE. It said it should be classified under 4-f, didn't it?

Dr. TODHUNTER. Unfortunately, we had no authority to take that action and so that had to be declined, the science aside.

Mr. GORE. Didn't PRL-1 recommend that it be classified as 4-f?

Dr. TODHUNTER. I do not care what it recommends, if it recommends something contrary to law.

Mr. GORE. Well, now the point is not a complicated one. PRL-1 recommended that it be classified under 4-f. Your memorandum recommended that it not be classified under 4-f, and you are saying that there was no need for anybody to review your memorandum because it was just drawn from the PRL-1. They say it is black; you say it is white. You say, "I do not need any review of my conclusion that it is white because I have just drawn from this document that says it is black."

Dr. TODHUNTER. Sir, first of all I am not sure that PRL-1 actually made a recommendation. There were attachments to it in the form of draft Federal Register notices that contained the recommendation to which you refer.

Second, the technical documents and the staff recommendation of September 11 had already quite clearly made the point that we did not feel that this was subject to 4-f. Therefore, it is quite plain that the update I prepared was nothing new for the agency. We already knew this.

Mr. **Walker**. Will the chairman yield?

Mr. **Gore**. Yes, I will.

Mr. **Walker**. Let's make very clear here what was in the PRL–1. It seems to me that you have made reference to the fact that there was a violation of law involved here. I think we ought to clarify that. The document recommended a 2-year study—is that not correct—with regard to section 4–f, which of course would be entirely contrary to law because the law would require a regulation within 180 days. Isn't that correct? Therefore, the recommendation referring to 4–f is just entirely contrary to the law, the way the law is written.

Dr. **Todhunter**. That is our understanding.

Mr. **Walker**. I thank you.

Thank you, Mr. Chairman.

Mr. **Gore**. Well, the point is that Dr. Todhunter says his memorandum is based on the PRL–1, and in fact it does not appear to be. The specific recommendation attached to the PRL–1 states, and I will quote:

> We believe that the statutory criteria, even when interpreted in a manner that would provide EPA a substantial degree of discretion in administering section 4–f, have been satisfied, and therefore recommend that EPA designate section 4–f as applicable to formaldehyde.

However, to keep the focus on the science of it, let's just examine your February 10 memo and look and see whether it is based on the PRL–1. By way of preface, you have conceded that nobody reviewed it. Nobody in your agency reviewed it. Did any outside group review it?

Dr. **Todhunter**. I do not know who would have reviewed it prior to its release.

Mr. **Gore**. Well, did you give it to anybody to review?

Dr. **Todhunter**. I sent it to the gentleman who I indicated in my testimony, for review.

Mr. **Gore**. What gentleman?

Dr. **Todhunter**. I will have to go back into the testimony here. I specifically sent it to Dr. Steven Sternberg at the Sloan-Kettering Memorial Cancer Center; to Drs. Gibson and Swenburg at CIIT; and to Dr. Maickel, who reviewed it with Dr. Carlson at Purdue University.

Mr. **Gore**. Well, those are all dated May 12 and May 14. Did anybody review it before you sent it to the Administrator?

Dr. **Todhunter**. Not to my knowledge.

Mr. **Gore**. Not to your knowledge. Did you give it to the Formaldehyde Institute?

Dr. **Todhunter**. Not before it went to the Administrator.

Mr. **Gore**. Did you review its substance with the Formaldehyde Institute?

Dr. **Todhunter**. Not to my knowledge, no, sir.

Mr. **Gore**. Now wait a minute. Did you have any conversations with the Formaldehyde Institute reviewing the substance of your memorandum before you sent it to the Administrator?

Dr. **Todhunter**. Well, the reason I state that that way is because, as I said, I did have personal communications with Drs.

Swenburg and Hech, who are at CIIT, on points contained in the memorandum. Now they have also been brought into things at the request of the Formaldehyde Institute, so I do not want to paint that inappropriately but to my knowledge no one at the Formaldehyde Institute has any particular reason to comment on the substance.

Mr. GORE. OK. These things from these people are just memorandums of telephone conversations prepared by you saying that these people called you on the telephone in May and told you such-and-such about your memo. We do not have anything from them, and what you were reading from earlier, apparently, now that we see it, is your own memorandums for the record and your own quotations of these conversations as you remember them.

Dr. TODHUNTER. The memoranda does indicate that copies have been sent to the people in question, and the memoranda also indicate that notes or letters will be following from those people.

Mr. GORE. Well, now, let's examine the February 10 memo. On page 5 you state, "I concur with the recommendations of OTS staff that formaldehyde does not meet the criteria of section 4-f for the following reasons," and then you go on to explain the criteria for your decision. Now when you refer to the recommendations of OTS staff, are you citing the staff recommendations of Mr. Clay that reversed Dr. Mueller's recommendation, or are you citing the staff technical papers?

Dr. TODHUNTER. The recommendation I was referring to was the September 11 memorandum of Mr. Clay.

Mr. GORE. Now let's examine some of these citations. You cite as a staff recommendation that:

> There is a limited but suggestive epidemiological base which supports the notion that any human problems with formaldehyde carcinogenicity may be of low incidence or undetectable.

Dr. TODHUNTER. That is not a proper characterization of the recommendation. I did not cite that as a staff recommendation; I merely cited that as being in the staff documents. That epidemiological data base is there. One can argue as to whether it is conclusive for demonstrating that there is no problem with formaldehyde. One can argue whether it allows some problem. The point being made in the memorandum is that whatever the magnitude of the problem, it certainly was not detectable by that method.

Mr. GORE. Well, you say that is not accurate, Dr. Todhunter, but that is from your memo. I am quoting from your memo on——

Dr. TODHUNTER. What you said, sir, if I recollect, is that the staff recommendation I referred to said that. That certainly is not what the memo said.

Mr. GORE. You said you concur with it. Let me just read it.

Dr. TODHUNTER. I concur with the staff recommendation, and then I provide a variety of reasons why I would concur with the staff recommendation. Now those reasons do not have to be the same as all the reasons used by the staff.

Mr. WALKER. In other words, these are your opinions?

Dr. TODHUNTER. Some of them are.

Mr. WALKER. You are providing those opinions as a scientist. Is that correct?

Dr. TODHUNTER. That is correct.

Mr. WALKER. This information is being given to the Administrator through Dr. Hernandez for review, and you are providing them with data on which to make a decision. Is that correct?

Dr. TODHUNTER. No, sir. The recommendation had already been sent up on September 11. I was updating the Administrator, as I mentioned earlier, for the purpose of simply going back and reiterating the fact that we did not think this was a 4-f as yet.

Mr. WALKER. However, the question here with regard to where the chairman is, is whether or not you as a scientist have a right to make that statement.

Dr. TODHUNTER. Oh, I should certainly think so.

Mr. GORE. Well, now, you say that you concur with the recommendations of the staff for the following reasons.

Dr. TODHUNTER. That is right. Those are my reasons for concurring. They are not necessarily the staff's reasons for making the recommendation on all points.

Mr. GORE. Well, if you concur with their recommendation, it is a little unusual to then cite a statement that is contrary to what the staff advised you, isn't it? I mean, that is a little——

Dr. TODHUNTER. I did not do anything of the sort, sir.

Mr. GORE. Well, yes, you did, and let me tell you why I think so.

Dr. TODHUNTER. Well, sir, you can think what you like but that is not what we did.

Mr. GORE. Let me tell you. You say, and I quote:

> There is a limited but suggestive epidemiological base which supports the notion that any human problems with formaldehyde carcinogenicity may be of low incidence or undetectable. It would not appear reasonable to say that a significant risk situation exists from these data.

Dr. TODHUNTER. That is a scientific opinion.

Mr. GORE. All right. You cite that as a reason for concurring with the recommendations of the OTS staff.

Dr. TODHUNTER. That is one of my reasons for concurring with their recommendations.

Mr. GORE. Now the OTS staff said something very different from what you said there. They said:

> This lack of a pattern, the lack of precise information concerning the number of persons exposed to formaldehyde and the level of exposure, and problems of confounding exposures, make it difficult to interpret these reports. Findings of excess cancers among workers in occupations and industries associated with formaldehyde and other chemicals raises concern that formaldehyde may be a carcinogen.

Now that does not say that the carcinogenicity may be of low incidence or undetectable, does it?

Dr. TODHUNTER. The staff had their own reasons for coming to the recommendation that they made, and I have my own reasons for concurring with that. In some areas those reasons may overlap; in some areas they may not.

Mr. GORE. In some areas they may conflict.

Dr. TODHUNTER. The staff recommendation, regardless of what the staff paper says as to the value of the epidemiological studies, nonetheless is that this was not a section 4-f.

Mr. WALKER. Will the gentleman yield?

Mr. GORE. I will yield, yes.

**Mr. Walker.** We do that all the time around here. We can both vote on a bill a certain way, and have entirely different reasons for arriving. We concur in what we do in terms of the vote on the bill, but I can vote on a bill because it spends too much money, you can vote on a bill because you think it spends too little money. The result of what we do is that we have concurred but for entirely different reasons. I do not think that is so unusual at all.

**Mr. Gore.** Well, this is not a political process. It is a scientific process.

**Dr. Todhunter.** There is always room for discussion in science, at least I should hope so.

**Mr. Gore.** Let me finish, Dr. Todhunter, please.

It is a scientific process and I do not think it would be good for the scientific process at EPA to be conducted in a political manner.

**Mr. Walker.** Well, if the chairman would yield further, we heard from our witnesses this morning that we cannot even come up with good enough science to decide whether or not we ought to ban this substance, so I think that there is plenty of room for some discussion about the science involved in all of this and that there can be a variety of interpretations about the science that is available.

**Mr. Gore.** Well, I would certainly refer anyone reading the record to refer back to Dr. Nelson's response on the question of banning it.

I would like to quote from the——

**Mr. Walker.** Well, Mr. Chairman, if you would yield further——

**Mr. Gore.** I will yield.

**Mr. Walker.**We have one scientist here who is disagreeing with other scientists. That is entirely acceptable within the science community, or I did not realize that science was walking in lock step on all of these things. It seems to me that here is an area where we have very definite disagreements about some of the interpretations of science. We have a couple of different interpretations here. That does not seem to me to be unusual in science, just like it is not unusual in politics.

**Mr. Gore.** Well, what is unusual about this particular small point, this involves the epidemiological evidence. Dr. Todhunter has stated, told the Administrator in what appears to be a decision document, that the epidemiological evidence indicates that there is no increased risk to human beings. There is not really much of an argument about that. There are two people who say that, Dr. Todhunter and the Formaldehyde Institute. The rest of science takes a contrary view.

In fact, your own epidemiologist on the staff responsible for this work left EPA and, upon leaving, wrote the following memo:

> Before leaving, I would again like to emphasize that the available epidemiologic data from studies on formaldehyde exposure are inconclusive and not supportive of no association, as purported by the Formaldehyde Institute.

Your own staff, the scientists in the field familiar with this evidence, take one view. The Formaldehyde Institute takes another, and you say, "I agree with the staff," and then you cite the view of the Formaldehyde Institute as a reason for supporting your decision.

**Mr. Walker.** Well, if the chairman would yield, it seems to me that the chairman is characterizing this a little bit differently, too. I cited this morning that the American Cancer Society agrees with the science here.

**Mr. Gore.** Well, they do not agree with the science here.

**Mr. Walker.** I referred to a study that the Du Pont Co. now has that indicates that they would agree with Dr. Todhunter's assessment, so there seems to be considerable disagreement within the scientific community that goes way beyond the Formaldehyde Institute. It seems to me that what we are into here is the politics of science and whose decision base you are going to use.

**Dr. Todhunter.** Mr. Gore, if I might respond in part to your question, the matter of epidemiological data is not central to the question of whether or not this poses significant risk. It certainly is a peripheral issue which we believe casts some light. Now certainly some scientists which have appeared this morning have taken one view, as I have indicated in my statement. Other scientists might take a different view.

I should like to submit to the record a study which appeared recently in Lancet, a very prestigious British journal, the conclusion of which states—and these are from scientists with the Danish Cancer Registry for the Institute of Cancer Epidemiology cn lung cancer risks from formaldehyde—

> Although our present results are based on small numbers, this examination also shows that long-term formaldehyde exposure in man is unlikely to carry an important risk for lung cancer. The absence of an increased lung cancer risk indicates that the examination of a possible carcinogenic risk to man from formaldehyde should be concentrated on more proximal parts of the respiratory tract, i.e. the nasal cavities, a target for which there is so far no evidence of an increased risk in humans.

Therefore, certainly there is a fair amount of debate within the scientific community. I do not think it would be accurate to say that we all——

**Mr. Gore.** On what?

**Dr. Todhunter.** As to whether or not the epidemiology supports that there would be a significant risk.

**Mr. Gore.** Now, wait a minute, wait a minute. That is the difference. Wait a minute, Dr. Todhunter. Of course, there is a debate about the nature of the evidence but there is no one other than you and the Formaldehyde Institute who say——

**Dr. Todhunter.** Sir, I just read you the——

**Mr. Gore.** Please, Dr. Todhunter, let me finish my statement and then you can respond. There is no one other than you and the Formaldehyde Institute who says that the epidemiological data indicates that there is no increased risk.

**Dr. Todhunter.** My statement was that the data did not support that the risk would be significant. You could not say it from those data. I just read to you an article in a peer review journal which indicates the same thing, so you cannot say that only I or the Formaldehyde Institute disagree.

The question of significant risk, as I indicated in my testimony, gets into the issue of are we talking about high risks or low risks. Now for the risk numbers which were indicated, the risk distributions in my February 10 update memorandum, these in fact were drawn from the risk numbers developed by OTS staff which fell out of the PRL-1 document, which had been developed in concert with the IRLG. They were numbers, the same numbers used by other agencies looking at this: FDA, OSHA, CPSC.

Now we indicated that the bulk of the risks that we looked at for our jurisdictions were somewhere below the range of 10 to −4, many of them around the range of 10 to −5. Now there are several types of risks which are everyday cancer risks which we might compare that to, to examine this question. Is this significant? In "Risk-Benefit Analysis," by Crouch and Wilson, who are respected scholars in this field, which is published by Harper and Roe, there are at least five risks which are higher than that 10 to −5. For instance, the risk to an airline pilot from excess cosmic radiation is 286 times higher than the 10 to −5 on an annual basis. A person who flies coast-to-coast every year once a year is about seven times higher at risk than that 10 to −5. If you fly from coast-to-coast once per week, if you are a businessman your risks are about 70 times higher. If you live in——

Mr. GORE. Dr. Todhunter, for Federal agencies normally risk factors that fall into the 10 to −4 and the 10 to −5 category have been found to be cause for concern. Is that correct?

Dr. TODHUNTER. Not entirely. No, sir. The Environmental Protection Agency, the FDA said there are tolerance levels for various actions to 10 to −5. Occupational safety risks are normally driven down to 10 to −4. These are target ranges.

Mr. GORE. Well, that is what I just said, 10 to −4, 10 to −5, that is the area at which concern arises——

Dr. TODHUNTER. No, sir, that is the area——

Mr. GORE. Well, what about chlordane? Chlordane was 10 to −4. Heptachlor was 10 to −5.

Dr. TODHUNTER. Chlordane was acted on for a variety of reasons, not the least of which is its environmental persistence.

Mr. GORE. Well, let me read you your statement. You say in your memo:

> Assuming that risk of some magnitude does exist, the calculated relative risks tend to fall into ranges which normally are of from low priority to no concern, such as those discussed in the section immediately above on the applicability of TSCA section 4(f).

Dr. TODHUNTER. That is correct.

Mr. GORE. However, the latest version of the technical document dated March 10 lists risks as high as 5.6 times 10 to −3, 5.6 deaths per 1,000. Do you believe that that is a range that is of no concern?

Dr. TODHUNTER. Sir, if that were the risk that we would substantiate, that would be great concern to us. That risk arises from a midpoint exposure estimate of 4.58 ppm in pathologists, and quite frankly, staff is not comfortable that that in fact is what they see.

Dr. Griesemer, who was here earlier, indicated that he might have seen as high as 2 ppm in his professional career, so that is one of the reasons why the staff has always proposed that what we need to do is to go out and verify some of the higher selected exposures to see if, in fact, they are representative because quite frankly, on the face of it, they sound a little bit high.

Mr. GORE. Well, I mean, it is not unique. There is another category, 3.67 times 10 to −4; 8.32 times 10 to −4; 2.92 times 10 to −4—

that is 3 deaths per 1,000 people. That is a significant level of risk, isn't it?

Dr. TODHUNTER. Sir, those risks, as I indicated in my testimony, some fraction of people may see higher exposures. That is why we have always said we need to go back and get better exposure numbers to be sure if that is correct, to see if that is in fact what is there. We are looking at numbers that have been generated using some 16 different collection methods and a variety of analysis techniques, and we are quite frankly not sure what those mean.

Now we have taken the assumption that they are, on their face value, the general distribution of risk, remembering that we have under our jurisdiction primarily general exposures through ambient air and water which generally do not support for most uses, as I indicated in my testimony, that there may be a significant risk. There are some areas where we might have concern. We want to examine those. We are revisiting them. We have a plan in action. We are going to confirm that.

There are some areas which are under the jurisdiction of other programs within our purview which we have already referred for further risk reduction analysis.

Mr. GORE. Now you say in your memo—and let's just pin this point down—"In terms of individual lifetime cancer risks, the various Federal agencies do not tend to regulate risks of 1 times 10 to −5—that is, 1 in 100,000—or lower, and tend to be ambivalent about risks between 1 in 10,000 and 1 in 100,000." Do you think that is an accurate characterization of the practice in Federal agencies generally?

Dr. TODHUNTER. It is not only an accurate representation but it is also the statement contained in the options paper developed by staff and appended to the September 11 memorandum of Mr. Clay.

Mr. GORE. Well, we had Dr. Upton here yesterday, the former director of NCI. He said that Federal agencies have generally been concerned with risks in the range of 1 times 10 to −5 up to 1 times 10 to −6, or risks of 1 in 100,000 or 1 in 1 million. Is there an official policy decision in EPA to be ambivalent about risks in the 1 in 10,000 range?

Dr. TODHUNTER. It would be inappropriate to set specific cutoffs to be used as generic guidelines. This is one of the problems——

Mr. GORE. Well, you have just done that.

Dr. TODHUNTER. Sir, if you may allow me to finish——

Mr. GORE. Go ahead.

Dr. TODHUNTER. We have gotten ourselves into boxes in the past by this attempt to try to regulate everything generically. The concept of saying that one carcinogen is the same as another is exceptionally simplistic and it is not founded in scientific reality.

Now the agency's general posture has always been and always will continue to be that regardless of the level of risk, if we believe that we can make a positive public health impact by taking action we will do so. In these particular cases for those areas where we have jurisdiction, we are not certain, we are not convinced at all, we do not believe, we do not see anything which impels us to a priority rulemaking under sections which require a rather extensive rulemaking record, certitude of the exposure data. We are not certain that we are going to have a public health impact by going at this on a priority basis.

The question is not, is there any concern, is there any risk whatsoever. The question is, is this a 4(f), is this a significant risk, is this something that you are going to have public health impact and you have to go out there, you have to take care of it.

In this particular case, the judgment of the staff cannot be supported to have ever been other than, we need exposure data, it is not good exposure data. Maybe some of these things might pose a problem but we have to pin that down. That continues to be our position.

Mr. GORE. Well, you see, the problem is that you are in charge of making these decisions. What does it say about the scientific process at EPA when there is no peer review of this kind of decision, there is not even any staff review of the decision, there is no——

Dr. TODHUNTER. The staff would not review this stuff.

Mr. GORE. Pardon me?

Dr. TODHUNTER. The staff would not normally review a policy decision.

Mr. GORE. Would staff normally review the science that goes into a policy decision? Is it going to be your policy not to let them do that?

Dr. TODHUNTER. The staff had already made its recommendation. Whether I concurred with it or not was immaterial from that standpoint.

Mr. GORE. However, you speak for the agency on the science questions, and if you are going to unilaterally change the science that the agency uses to arrive at a decision, without peer review, without staff review, and then you have your judgment called into question by scientists of the eminence of those on the prior panel, then what does that do to the scientific process at EPA? It calls it into question and it leads to the appearance that the Formaldehyde Institute's view of the scientific questions had an inordinate influence on your view of the scientific questions.

Dr. TODHUNTER. It does not lead to any conclusion of the sort, sir. The science has not been changed in any aspect. The risk estimates prepared by the staff are the basis for which the policy decision on whether this was section 4(f) or not was made. That was made back on September 11. That recommendation went forward from Mr. Clay. Those estimates are still there. We still stand on them. We are proceeding in the direction we have always intended to proceed, which was to get some of that information. Now I have taken a policy decision in fact and I have indicated that the pesticide program should be looking at risk reduction measures for certain pesticidal uses of formaldehyde, which they are looking into. It is not clear that those uses are still around but, by God, I am not going to sit around where I see an area where this agency can make a public health impact and wait for something to happen. I have that responsibility to the American people but I also have the responsibility not to lead them down on a wild goose chase until we see what we are doing, until we see the scope of the problem.

Our staff has always said that the scope of this problem is indeterminate. We need that exposure information and that is why I am committing the Office of Pesticides and Toxic Substances to go out and get it.

Mr. **Gore**. Let me read you another scientific judgment that you made in your memo. On page 11 you say, "It has not been possible to demonstrate a statistically significant difference in exposure levels in urea formaldehyde foam homes as opposed to non-UF homes." What data did you use to determine the lack of any statistical significance there?

Dr. **Todhunter**. That was drawn from a decision in a court case in Massachusetts on the banning of formaldehyde foam in Massachusetts.

Mr. **Gore**. Did the Formaldehyde Institute provide that for you?

Dr. **Todhunter**. I do not know who provided it for me. I asked someone to get me a copy of the decision in question.

Mr. **Gore**. How did you hear about that?

Dr. **Todhunter**. It was in the papers.

Mr. **Gore**. Well, who did you ask to get it for you?

Dr. **Todhunter**. I asked possibly Mrs. Vogt of my staff or possibly Dr. Hill. I do not recall.

Mr. **Gore**. Do you know if they got it from the Formaldehyde Institute?

Dr. **Todhunter**. I haven't the slightest idea. It showed up on my desk one morning.

Mr. **Gore**. Did Mr. Byington ever mention this court case to you?

Dr. **Todhunter**. Subsequent to my February 10 memo he did mention it to me, yes.

Mr. **Gore**. Might he have mentioned it to you beforehand?

Dr. **Todhunter**. No, I do not think so, because we did not talk about it——

Mr. **Gore**. Well, you said before you were not sure whether you had talked or not.

Dr. **Todhunter**. No. I said before I had asked to get information as to how to contact Dr. Hech, and I am sure I did not discuss the court case with him at that time.

Mr. **Gore**. You could not have done that in between "hello" and "goodby" on January 26?

Dr. **Todhunter**. I think the court case—actually I do not remember when the court case came out. It may have been impossible, even, because of the time. I certainly did not discuss it with him.

Mr. **Gore**. Relevant to that court case, the State in question did ban the substance.

Dr. **Todhunter**. Yes, but the decision of the judge overturning the ban made that statement and that is where I drew that from.

Mr. **Gore**. Now are you relying on this one court case against the scientific abilities of your staff? We had testimony here just in the prior panel from one of your peers in another agency who said just flatly that this statement is incorrect. It is just wrong.

Dr. **Todhunter**. Sir, the reason that Dr. Preuss made that remark is for one reason: At the time that the foam is installed, as he indicated, and we agree, there may be some difference in complaint homes in the level of offgassing. However, our consideration has to do with protecting people over a long-term basis and, as Dr. Preuss clearly indicated, after some time these levels do decay to background levels and one cannot really tell a difference, so I do not see any inconsistency there.

We are talking about different points in time and where our regulation would step in. There are different jurisdictions.

Mr. GORE. Well, again it illustrates the problem of using a scientific procedure that does not have any peer review, does not have any staff review, at the same time that you are talking on the telephone with the lawyer for the industry that is going to be cost money by this, and saying "hello—goodby" a week ahead of time over at the—was that at the Holiday Inn on January 26?

Dr. TODHUNTER. It is the place right there around from the agency. I think it is a Holiday Inn.

Mr. GORE. Now another subcommittee asked you about that——

Dr. TODHUNTER. Yes.

Mr. GORE [continuing]. And you erased that from your——

Dr. TODHUNTER. No; I did not.

Mr. GORE. You did not?

Dr. TODHUNTER. No, sir. The subcommittee had a log which they prepared on their own, and the accuracy of that was not something I had any control over.

Mr. GORE. Oh, that was an earlier meeting that was erased from your calendar, a November meeting.

Dr. TODHUNTER. November? No; I am not aware of a meeting like that.

Mr. GORE. Well, what meeting was it that you erased?

Dr. TODHUNTER. I did not erase any meeting.

Mr. GORE. In documents provided to another subcommittee?

Dr. TODHUNTER. No, sir. The subcommittee on the day of the hearing in question produced—Mr. Moffett produced a list of things he claimed to be a log of my activities which had been, to my knowledge, prepared by his staff, and if that was inaccurate that is not my responsibility.

Mr. GORE. All right. Now let me go to the animal data. The Federal Panel on Formaldehyde—this is the Federal Panel report to the CPSC in November 1980—concluded "Free formaldehyde is not usually found in plasma or other body tissues in measurable quantities."

On page 8 of your memorandum to the Administrator you indicate that normal tissue contained significant levels of free formaldehyde. On what data do you base that?

Dr. TODHUNTER. It is an interesting point that you raise. First of all, whether the material is free or tied up as a tetrahydrofolate adduct or as a hemithioacetol with glutathione does not really much affect its ability to react with genetic material because that is an equilibrium system and——

Mr. GORE. What is the basis of that statement?

Dr. TODHUNTER. That is a basic, fundamental principle of biochemistry. Everybody knows that.

Mr. GORE. Well, can you cite any——

Dr. TODHUNTER. Good Lord, I can cite you any text in biochemistry that will tell you the same thing. If you have an equilibrium system, the——

Mr. GORE. Could you provide the citation for the record, please?

Dr. TODHUNTER. I will be more than happy to do so.

Mr. GORE. All right. Without objection, we will hold it open.

Dr. TODHUNTER. Fine.

Mr. GORE. Now your statement is contrary to what the Federal panel that was convened on this subject stated and——

Dr. TODHUNTER. Yes.

Mr. GORE [continuing]. I ask you what you cite as the basis for your view, which is diametrically opposed to the panel of scientists that studied this subject, and you are saying that it is just elementary chemistry?

Dr. TODHUNTER. No, sir. The free formaldehyde I was referring to in the memo was that which was not tied up as the glutathione adduct, and I had discussed with Dr. Hech his measurements. He indicated between anywhere from 10 to 40 percent would not be tied up as that form. That was an oversimplification on my part to refer to it as "free." You must remember that this was not written primarily as a scientific document but as an update for the Administrator which would let her know various areas——

Mr. GORE. It was not written as a scientific document?

Dr. TODHUNTER. It was not supposed to be a support document. That had already been prepared.

Mr. GORE. It was released as a support document. I mean, it was released to the press as an explanation for the decision. It was cited by the Deputy Administrator to the White House science adviser as the basis for the decision, and you as the chief scientist—you, speaking for the scientific staff of EPA, had the responsibility for doing this, and it is not a scientific document?

Dr. TODHUNTER. It is a combination of policy and science, as you see in the document. Now that was written really for a lay reader and——

Mr. GORE. Is this a science question or a policy question, the——

Dr. TODHUNTER. Whether it is 4(f) is certainly a policy question.

Mr. GORE. No; that is not what I asked you. Is the question of the levels of free formaldehyde in normal tissue, is that a policy question or a science question?

Dr. TODHUNTER. That is a question of science and, as I said I had discussed with Dr. Hech, the level not bound to glutathione because this was what he felt was an important adduct. Of course, there are tetrahydrofolate adducts of formaldehyde which also pick up a portion but even so, possibly up to 2 percent or so, formaldehyde would be free. At any point the question of whether it is free or not is irrelevant.

Mr. GORE. Well, why do you make it, then? Why do you make this statement?

Dr. TODHUNTER. Simply because I had that information from Dr. Hech and I wished to point out that some of the formaldehyde might be tied up and some might not, that simple observation.

Mr. GORE. Were you present at this science court thing where the industry came in with EPA?

Dr. TODHUNTER. As I indicated, I was at two out of three.

Mr. GORE. This question came up at that meeting, at one of those science courts, didn't it?

Dr. TODHUNTER. The free formaldehyde?

Mr. GORE. Yes.

Dr. **Todhunter**. Yes. I believe it did, and Dr. Hech indicated at that time that some portion was bound to glutathione.

Mr. **Gore**. Well, a witness is coming up, and I apologize to him for taking this from his statement. He says, and I quote, at the science court meeting

> Dr. Hech implied that this was free formaldehyde. During a break in the meeting, I asked Dr. Hech if it was not in fact more likely that formaldehyde was found as an adduct to tetrahydrofolate or glutathione and therefore unavailable for interaction with the cellular constituent. He stated that this was probably true and we apprised Dr. Hernandez of that fact.

Yet you went ahead and stated the opposite in your memo. This was not reviewed by the staff or reviewed by peers, either. Correct?

Dr. **Todhunter**. The memo was not reviewed by the staff. That is correct.

Mr. **Gore**. Again, I just think it calls in serious question the quality of science that is used to support a decision of enormous importance, with 26 million Americans at elevated exposure to this chemical and the other Americans who come into contact with it in a ubiquitous, in a regular way.

Now in the Clay memorandum to you of September 11 there are two tables entitled "Estimates of Numbers of Cancer Cases, Including Upper 95 Percent Confidence Limits for Those Estimates." Why did you change the technical document to eliminate the upper 95 percent confidence limits?

Dr. **Todhunter**. I will let Mr. Clay answer that question because——

Mr. **Gore**. No, no. He prepared the original one and you——

Dr. **Todhunter**. Well, I did not change it so any changes went on at the staff level. Therefore, I am not the person who could answer that question. I haven't the slightest idea why they changed one thing or another. As a matter of fact, I believe at one point I indicated that we should be sure to have around the 95-percent upper confidence limits but Mr. Clay can more specifically address that issue.

Mr. **Gore**. All right. Mr. Clay?

Mr. **Clay**. Thank you. Let me clarify the staff decision on the documents. What we are talking about is the September 11 cover memorandum, and we are talking about an options paper on formaldehyde which was attached. Then there was the original PRL-1 document that was attached, the one from early February. All those were transmitted forward so the PRL-1 was the same PRL-1.

The change in numbers from the staff standpoint, once we had made our recommendation and there was the threat of the lawsuit, what we then decided to do was to update the PRL-1 document which had been generated the previous February. The PRL-1 document was then rewritten on November 16, retitled the "Technical Document," also on February 19 and also on March 16. In each of those cases the staff would update in terms of the more recent exposure information they had and use different models. As a matter of fact, one version took all the numbers out, the February version, and then we put them back in in March. However, it was in anticipation of not in making the decision but in defense of a potential lawsuit that we were revising the technical document.

Mr. Gore. Now the dropping of the high and low estimates tends to understate the risk, does it not?

Mr. Clay. Well, no, I do not think so.

Mr. Gore. It does not tell you what the high bound of the risk may be, does it?

Mr. Clay. Or the low bound, either.

Mr. Gore. Well, we had testimony from Dr. Crump, who said that he thinks that that is the normally accepted way of comparing these different risk estimates, to look at that high bound.

Dr. Todhunter. There are a variety of opinions on whether one should use the upper bound. The risk distributions in the February 10 memo, in fact, were based on the 95-percent upper confidence limits. Whether they are in Mr. Clay's memo or not is not pertinent to the February 10 memo.

Mr. Gore. Agencies normally use the high, the 95-percent confidence limits, right?

Dr. Todhunter. We would use those as a comparison even if we were trying other models. As you know, there are some——

Mr. Gore. However, you did not put them in the document.

Dr. Todhunter. Which document? Actually, I think they are currently in the technical document.

Mr. Gore. In the latest technical document?

Dr. Todhunter. I think the upper confidence——

Mr. Gore. They are not in the latest technical document, are they?

Dr. Todhunter. I do not know. I have not looked at it recently.

Mr. Gore. Well, you revised it, didn't you?

Dr. Todhunter. My staff did, sir, yes.

Mr. Gore. Why have you changed the format in the March 10 technical document to go back to risk numbers rather than numbers of cancer cases?

Mr. Clay. Again, we were revising the document in anticipation of going to court and we thought that would present a better case.

Mr. Gore. All right. Now let me go to the question of irritation, animal data. On page 8 of your memo to the Administrator you note that the hyperplastic metaplastic effects of formaldehyde exposure were reversible. The final CIIT report released on December 31, 1981, states that some postexposure animals developed cancer of the nose. Considering this new observation, would you think it appropriate to amend your assessment of the carcinogenic potential of formaldehyde?

Dr. Todhunter. First of all, my assessment of the carcinogenic potential of formaldehyde has always been, and I have always stated that I believe it to be an animal carcinogen. The rat is apparently very susceptible to formaldehyde. There is some limited evidence in the mouse. I have always presumed that it may pose a risk to humans under appropriate exposure conditions so in that sense, no, additional evidence would not cause me to go back and reassess that decision.

Mr. Gore. I am asking a specific question: You state that the hyperplastic and metaplastic effects were reversible. Do you want to amend that?

Dr. Todhunter. At the low doses, that is what it states.

Mr. **Gore**. Do you want to amend that in light of the fact that the final CIIT report——

Dr. **Todhunter**. No, they were still reversible.

Mr. **Gore**. Let me finish the question, please.

Dr. **Todhunter**. Oh, I am sorry.

Mr. **Gore**. The final CIIT report states that some postexposure animals developed cancer of the nose. Considering this new observation, do you still stand by your scientific statement in your memorandum to the Administrator, that it is reversible?

Dr. **Todhunter**. I still stand by the statement that at the lower exposure levels it was reversible because that is still the observation of CIIT.

Mr. **Gore**. Why do you consider the hyperplastic effects and metaplastic effects to be mitigating factors in the carcinogenicity of formaldehyde?

Dr. **Todhunter**. Well, that is a somewhat detailed argument. I will be happy to go into it if you will give me the time to do it. It is a little bit lengthy. It has to do——

Mr. **Gore**. Does the memo explain that at all? It does not——

Dr. **Todhunter**. No. As I indicated, the memo was more intended for a lay person.

Mr. **Gore**. Is it fair to state that your view on that is an eccentric one that is not shared by most scientists?

Dr. **Todhunter**. Not at all, sir.

Mr. **Gore**. Well, the earlier panel stated that they felt that to be the case.

Dr. **Todhunter**. Well, let's talk about the specific issue which you raised, OK?—why I believe that hyperplastic and metaplastic effects might——

Mr. **Gore**. Well, I do not want to get into a detailed discussion. I want to talk about the sores in the animals' noses. You imply that there were sores in the animals' noses. Are you aware that no such sores were reported in the final report from CIIT?

Dr. **Todhunter**. Sir, there were alterations in the early part of the exposure of the animals. Now the question that there were sores in the noses and then tumors developed later on is admittedly an oversimplification, again for a lay person. I am just trying to fix the sequence of events here. The sores in fact did subsequently heal up. However, there were metaplastic and dysplastic lesions.

Mr. **Gore**. Does that cause you to amend your assessment of the carcinogenicity of formaldehyde?

Dr. **Todhunter**. No, sir, it would not because the concern I had was not with whether or not there were a discreet threshold for the carcinogenicity in the rat but rather with the shape of the dose response curve, which is markedly nonlinear in the CIIT study. Now the——

Mr. **Gore**. Did you review the CIIT study on this point? Is that the source of your statement here?

Dr. **Todhunter**. Yes, I spoke with Dr. Swenburg on that point.

Mr. **Gore**. However, you did not look at the data yourself?

Dr. **Todhunter**. No, sir, I did not look at the data myself.

Mr. **Gore**. You just took this guy's word for it?

Dr. **Todhunter**. No, sir. Other than what was contained in the release which the CIIT had made to the international agency working group——

Mr. **Gore**. Therefore, you took—this is an industry group, right?

Dr. **Todhunter**. I do not know if that would be appropriate, to characterize it that way, but they are funded by member companies.

Mr. **Gore**. Paid for by the industry. I mean, it is a respected group. I respect them and I think everybody in the field does but it is an industry group, and your testimony here is that the basis for your statement here is a statement to you by a scientist with this industry group. You put it right in your memorandum to the Administrator—no peer review, no staff review.

Dr. **Todhunter**. There is no question that these animals had metaplastic and dysplastic lesions. Now that would not affect my overall assessment of the carcinogenicity because my overall assessment is that this is a demonstrated animal carcinogen, particularly so in the rat. That does not turn on that.

The question which I was examining, which I was thinking about at that time was, Why is the dose response so nonlinear? No in point of fact, the same sorts of thoughts are given in the Federal Formaldehyde Panel's report where they discuss the fact that cytotoxic agents have any number of mechanisms whereby they might enhance the carcinogenesis process. They stimulate cell division and there are a number of reasons why the ability to stimulate cell division would have an impact on the shape of the dose response curve. That is the only point that was being addressed. It is a well recognized set of observations. The Federal Formaldehyde Panel talks about the same concern. I simply raised the issue.

However, the question of whether or not this is an animal carcinogen does not turn on that because my assessment has always been, the bottom line from me and from the agency has always been that, yes, this is certainly producing cancers in rats. It certainly is.

Mr. **Gore**. Well, you referred to the IARC group a moment ago. Let me just read you their statement: "In summary, then, the IARC working group has declared that formaldehyde must be regarded as if it were carcinogenic to man on the basis of toxicological studies in animals."

Dr. **Todhunter**. We would agree with that. We certainly would, and that is why we went out and did all the way along, we have done risk analysis on it. If we did not think it was carcinogenic to man, if we did not think it had the potential, let us say, we would not bother to spend staff time to work these models over.

Mr. **Gore**. Now at one point, Dr. Todhunter, I believe that the Office of Toxic Substances received a review of your decisionmaking process on formaldehyde as well as DEHP by an outside management consultant. Isn't that correct?

Dr. **Todhunter**. I am not aware that we did. Mr. Clay, can you comment?

Mr. **Clay**. Let me clarify that. At one time we did, in anticipation of going off on a retreat for management purposes on how we were running the office, in particular how I was running the office, we were interested in learning from our past mistakes in the way we manage projects. We have a rather complex way of doing it. In anticipation of that retreat, we decided that we would in fact have two case studies developed with the understanding at the time that we were developing them that in order to insure frankness, that we would not retain copies.

Therefore, they were developed. We went off. We had a retreat. We discussed them, and to the best of my knowledge they were all destroyed.

Mr. GORE. That is interesting. They were paid for with taxpayers' dollars, were they not?

Mr. CLAY. Yes, sir.

Mr. GORE. It was a study by an outside management consultant of the decisionmaking process used by Dr. Todhunter on formaldehyde, and that study has been destroyed?

Mr. CLAY. It was not about Dr. Todhunter at all, sir.

Mr. GORE. It was about the decisionmaking process on formaldehyde?

Mr. CLAY. Yes, sir.

Mr. GORE. You do not know about it, Dr. Todhunter?

Dr. TODHUNTER. It did not concern my thinking on the subject. It was apparently strictly a staff review, a review of what the staff had done for their purposes——

Mr. GORE. Did you ever see it, Dr. Todhunter?

Dr. TODHUNTER. No, sir. There was no reason why I should have seen it.

Mr. GORE. Well, if we are going to spend taxpayers' money to review the decisionmaking process under you on this matter, I do not know why you would not be aware of it.

Dr. TODHUNTER. There are expenditure authorities which are properly delegated to the office directors. I cannot be down there reading every single contractor's report that comes in every time. We get a lot of them. All Federal agencies——

Mr. GORE. Did you go to the retreat in question, Dr. Todhunter?

Dr. TODHUNTER. No, sir.

Mr. GORE. You did, Mr. Clay?

Mr. CLAY. Yes, sir.

Mr. GORE. I see.

What is the current status of the Keyworth initiative to write the IRLG risk assessment document?

Dr. TODHUNTER. The current status is that the Office of Science and Technology Policy is getting various sections of a draft written by various Federal agencies, and then that will be circulated among Federal agencies and academic and institute scientists for comment and review.

Mr. GORE. What is the time frame on that?

Dr. TODHUNTER. If I recall correctly, I think right now they are thinking of some time in June having an initial draft that people can start commenting on and reviewing, something like that.

Mr. GORE. Will there be public review and comment?

Dr. TODHUNTER. Oh, certainly.

Mr. GORE. All right.

Now on October 28, 1981, the EPA Scientific Advisory Board recommended that the formaldehyde controversy be given to the National Academy of Sciences for review. Is that correct?

Dr. TODHUNTER. I believe it is.

Mr. GORE. Why didn't you follow that recommendation?

Dr. TODHUNTER. The recommendation was not made to me, first of all. I believe it was made as a request to Dr. Hernandez, and at that time—could you give me the date again, so I get the time frame better?

Mr. GORE. October 28, 1981.

Dr. TODHUNTER. OK. At that time, the Office of Toxic Substances staff had already worked up and gotten preliminary approval on a work plan for formaldehyde to go out and conduct the exposure investigations and further analyses that they felt were necessary to develop the proper regulatory responses, bearing in mind that we might also look at things other than just cancer because we had some concerns there.

That recommendation did not come back down to us. Presumably it may have stayed up with Dr. Hernandez. Subsequently, I believe that the Office of Science and Technology Policy has decided that various Federal agencies have a piece of this and the best way to approach it is to get them all involved. They are now coordinating this and as a part of that, we have been involved in trying to set up an information clearinghouse with the National Center for Toxicological Research. That is pretty much the way it has gone.

Mr. GORE. At what point do you anticipate making a decision on the waivers for the Chemical Manufacturers Association petition for exemption?

Dr. TODHUNTER. Which part of the exemption? They have several specific items they are petitioning.

Mr. GORE. Which ones are they petitioning for?

Dr. TODHUNTER. Well, they have petitioned for a polymer exemption for certain polymers, and they have also petitioned for a low-volume exemption similar to the exemption found in the European chemical law, and they have petitioned for an exemption for site-restricted intermediates, those which stay within the plant site. Those have been under development. I believe the polymer exemption is moving forward more quickly. Mr. Clay, since he has most of this right now, can address you more specifically.

Mr. CLAY. The site-limited, low-volume exemption is in fact ahead of the polymer one by about a month. It is in the other tower awaiting the Administrator's signature to be published for comment. The polymer one is about a month behind it. A draft has just gone into agency review and we will have the agency review by the first part of next week. At that time we will decide where we are at.

Mr. GORE. The first part of next week? OK. Do you have the consulting firm's evaluation of EPA's decisionmaking process on that issue?

Mr. CLAY. I am not familiar with what you—oh, you mean the early—no, sir, to the best of my knowledge the case studies they were all destroyed.

Mr. GORE. All right. That was destroyed also?

Mr. CLAY. Yes, sir.

Mr. GORE. Now on page 11 of your memo to the Administrator you talk about the epidemiology and you state that if formaldehyde were a potent human risk, it should show up epidemiologically.

How many people would have to be included in an epidemiological study before one could reasonably expect to see excess cancers due to formaldehyde?

Dr. TODHUNTER. It depends on the level of significance but normally one would like to have a cohort of at least 1,000 or 2,000 people to begin to get any good idea.

Mr. GORE. Do you believe that positive epidemiological data is needed before regulation of a chemical carcinogen is warranted?

Dr. TODHUNTER. Certainly not.

Mr. GORE. Pardon me?

Dr. TODHUNTER. Certainly not.

Mr. GORE. Certainly not? OK. You said 1,000 people would have to be included?

Dr. TODHUNTER. At least, before I would feel comfortable that that was really a good size study, if we are talking about——

Mr. GORE. To detect what level of risk?

Dr. TODHUNTER. To be able to detect something at the 95 percent confidence level and be certain you were seeing something, if you wanted to establish——

Mr. GORE. At what exposure level?

Dr. TODHUNTER. Pardon?

Mr. GORE. At what exposure level?

Dr. TODHUNTER. Oh, that depends. You know, if you are talking about a risk—most epi studies, for instance, they are often put forward in the terms of a relative risk and there are varying opinions on this but some people feel that differences of 5 or 10 percent are where you can begin to see really very clear-cut, decisive effects. That is usually the type of question that you ask if you want to know if something in fact—are we going to classify this as a known human carcinogen? It is not the kind of question that one necessarily asks if one is merely interested in looking at the epidemiological data base and saying, Is there some glaring problem here that we are not seeing? That is really where my comments were addressed to. I would certainly not ever put forward the position that one would need to wait for epidemiological data if you had good animal data that suggested you had a risk that you could address by some mechanism.

Mr. GORE. Well, everybody has told us that the epidemiology is extremely difficult and it is hard to pick up any kind of evidence from this. You say 1,000 people is all you need to——

Dr. TODHUNTER. No, sir. What I am saying is that if you wanted to have a really big study, at a minimum you would think you would have to talk to 1,000 people. The NCI——

Mr. GORE. A really big study would be 1,000 people?

Dr. TODHUNTER. No. Below 1,000 people I really would not have much confidence.

Mr. GORE. However, at 1,000 you would think that would be enough?

Dr. TODHUNTER. At that level and on up you would start to have greater confidence in the study as the study got bigger. The NCI study that is ongoing now is 17,000 people. This duPont study which we really have not had a chance to review covers about 7,000 people.

Mr. GORE. Well, do you think the NCI study is going to give us any kind of conclusive answers?

Dr. TODHUNTER. I think what the NCI study will do is, it will indicate that whether or not there are any glaring things there, and the question when you are talking significant risk, such that you want to put everything else aside , put everything else on the back burner to go after this one, is one where you really are looking for a problem that you can get your teeth into.

Now in this particular case we have other things that we are looking at. We have other carcinogens that are brewing on our kettle that we are concerned about, and we have to make some decision, some prioritization. Quite frankly, we think that for us to go charging after formaldehyde in terms of issuing a regulation right now without really knowing, without having any standard exposure methodology or information, would be premature. Given the fact that we have other carcinogens that we would rather get at first, we do not think that is a good selection of priorities, and that is all we are really doing here.

Mr. GORE. All right. Those are second bells over on the floor. I want to apologize to the witnesses who are waiting to testify. We will get to you very quickly. We are going to have to recess for 10 minutes and when we come back I will recognize counsel for the minority.

[Recess taken.]

Mr. GORE. The subcommittee will come back to order.

I would like to recognize Mr. Clement.

Mr. CLEMENT. Thank you, Mr. Chairman.

Dr. Todhunter, I would like to clear up a few things on the record, if I could. There was a considerable discussion earlier about the appropriate magnitude of risk to cause agency concern or to trigger agency regulation. I think the testimony by Dr. Arthur Upton yesterday was that he would be considerably concerned at risks in the magnitude of 1 times 10 to −5 or 1 times 10 to −6, down to 10 to −4. Is that an area that you at EPA would also be willing to say that the agency should be concerned about?

Dr. TODHUNTER. From 10 to −4 to 10 to −6 is an area where the agency normally gets anywhere from concerned and we had better have a look to see if there is anything happening, to an area where the agency would not show any particular concern. Many of the standard-setting practices of the agency, in fact, are targeted to about 10 to −5, and this happens in other agencies as well. OSHA, I believe, targets to around 10 to −4 or somewhat higher than that. It varies.

Mr. CLEMENT. What do you think would be the appropriate risk level to consider kicking off agency regulatory action?

Dr. TODHUNTER. Well, for any type of risk the appropriate risk level would be anyplace where you found an unreasonable risk. That is definitely a situation where you would weigh the risks against any health or economic benefits attendant on the use of the particular material. It is a decision which we face quite frequently in the pesticide program, and for various effects we sometimes take action. Sometimes we do not even need a human health effect to take regulatory action. If we have an environmental concern and we think it is unreasonable, we will take action on the basis of that.

Therefore, I would not like to get out and say, you know, there is a cutoff number but certainly in terms of setting priorities, which is what section 4(f) is about, we are looking at a situation where we have a variety of potential carcinogens which we may want to get into, and we are trying to set those which really need expedited rulemaking in order to address some outstanding problem that we need to get a handle on immediately. In that sense, I think that the risk that we have found from most of the uses of formaldehyde and certainly from the ambient air and water exposures just do not compel us in that direction toward anexpedited rulemaking.

Mr. CLEMENT. All right. Thank you, Dr. Todhunter.

Let's move on to another area, and that is one that caused me some concern earlier. There were at least implications that the Chemical Industry Institute of Toxicology is an industry-supported group. I would be willing to stipulate that that is correct. The CIIT is in fact supported by the chemical industry.

However, let me ask you, what type of a reputation do they have in the scientific community? Are they generally highly regarded?

Dr. TODHUNTER. They generally have an excellent reputation.

Mr. CLEMENT. In fact, the data that we have done a great deal of arguing over today is basically all generated by CIIT. Is that not correct?

Dr. TODHUNTER. That is generally correct.

Mr. CLEMENT. If in fact the data were terribly skewed—and there really have not been allegations of that but if there were—it would basically be an implication that the industry itself had shot itself in the foot. Would that be a fair assumption?

Dr. TODHUNTER. One would possibly conclude that.

Mr. CLEMENT. Well, let me go back to their data for just a moment. We are talking about a strain of rats in which there is a very high incidence of nasal cancers at exposures of 15 ppm. That is basically what the data shows, isn't it?

Dr. TODHUNTER. At 15 ppm the incidence rate is around 50 percent which is considered high. It is very high, especially since rats normally do not get nasal cancers.

Mr. CLEMENT. That incidence rate falls off rather quickly down to about 5 ppm. Isn't that correct?

Dr. TODHUNTER. At 5 ppm there were some two rats or so—it is about a 2-percent incidence rate, I am sorry, which CIIT in their analysis judged not to be statistically significant but which I would disagree with on that point. I think at least it is biologically significant. There was no incidence of malignant tumors found at 2 ppm and no malignancies of that particular type at the 0 ppm control.

Mr. CLEMENT. At 2 ppm and lower there was no incidence at all in rats. Is that correct?

Dr. TODHUNTER. That was not observed.

Mr. CLEMENT. Would you then say as a scientist that the curve on the incidence of nasal cancer in rats and formaldehyde is linear or nonlinear?

Dr. TODHUNTER. At the exposure ranges examined, the curve is markedly nonlinear at the observed dose response.

Mr. **Clement**. Could this lead to the assumption that in fact there is an entry-level plateau where the rats or other living beings might be able to tolerate a certain amount of formaldehyde before it kicks off the incidence of cancer?

Dr. **Todhunter**. I think it would be more accurate to say that it would suggest that the risk falls off as the dose decreases much more rapidly than one might assume using a linear extrapolation.

Mr. **Clement**. All right. Finally, let me ask you on this line of questioning, 15 ppm is a fairly high concentration of formaldehyde, is it not?

Dr. **Todhunter**. Yes.

Mr. **Clement**. What is the normal human tolerance for formaldehyde?

Dr. **Todhunter**. Well, humans can adapt. Certainly the evidence introduced in the CPSC proceedings indicates that at levels as low as a quarter of a part per billion there are irritant effects but humans can normally adapt and could probably tolerate exposures of 2 or 3 parts per million for some period of time but I certainly do not imagine that a human would tolerate an 8, or let's say, a 10- or a 15-ppm exposure. I think that would probably be too much to expect.

Mr. **Clement**. At between 3 and 5, perhaps, the discomfort would be so great that it would drive a human out of that concentration?

Dr. **Todhunter**. You certainly would not want to stay there for a prolonged period of time. However, because of adaptation to mouth breathing you might stay there for some short period of time.

Mr. **Clement**. Thank you, I think that at least clears up that question.

Mr. Clay, I would like to ask you, I understand that you were the director of the office that produced the original document that Dr. Todhunter has referred to as a decision document last fall. We have heard charges that changes were ordered in that document for political reasons. Are you a career employee of the agency?

Mr. **Clay**. Yes, sir.

Mr. **Clement**. Did you see any indications that changes were ordered for political reasons?

Mr. **Clay**. No, sir.

Mr. **Clement**. Did you see any changes that were made in that document, in the various drafts, that you did not feel comfortable with from a scientific point of view?

Mr. **Clay**. It was very clear that it was the office's document and we put into it what we felt collectively was what was required.

Mr. **Gore**. Will the gentleman yield?

Mr. **Clement**. Of course.

Mr. **Gore**. Are you a scientist?

Mr. **Clay**. I am a chemical engineer.

Mr. **Gore**. Do you feel capable of judging the biological——

Mr. **Clay**. No. I rely on my director of health and environmental review to do that.

Mr. **Gore**. Thank you. Go ahead.

Mr. **Clement**. All right, Dr. Clay, let me ask you——

Mr. **Clay**. It is not "Dr. Clay," by the way. It is "Mr. Clay."

Mr. CLEMENT. All right, Mr. Clay, did your director of science, below you, did he feel comfortable with the changes made in the science?

Mr. CLAY. Yes, to the best of my knowledge, they did. The actual document was prepared by my assessment division, which is the division we have that is in charge of pulling everything together. In the end, as we were going through the various versions of the document, we collected and did the best job we could and what we really wanted was in the document. That is what we did.

Mr. GORE. We are not talking about the Todhunter memorandum here, are we?

Mr. CLEMENT. No, we are talking about the——

Mr. CLAY. No, we are talking about the technical document which was the outgrowth of the PRL–1.

Mr. GORE. What I had said earlier was that the scientific judgments that were changed were in the Todhunter memorandum, changed from what the technical documents had contained.

Go ahead.

Mr. CLEMENT. Mr. Clay, in essence then your testimony is that you and the people in your office who were responsible for production of the technical memorandum do feel comfortable with the material which is contained in the current version, and feel it is fully defensible and supportable?

Mr. CLAY. Yes, sir. We always maintain we would like to have better exposure data, and we continue to do that but that is the best we have right now.

Mr. CLEMENT. All right. A final question for Dr. Todhunter. There was some discussion earlier about whether or not formaldehyde in tissue is free or bound. Let me ask you—I am not a scientist, I am a lawyer—is there really any difference in the reactivity between bound and free formaldehyde in the tissue?

Dr. TODHUNTER. That is a good question. The free formaldehyde would possibly be slightly more reactive on a rate basis. It being in an aqueous solution, of course, would probably be hydrated to the glycol form. That is a standard property of formaldehyde when it is aqueous solution.

The problem is that unlike many biological reactions which are mediated enzymatically because they normally would not occur rapidly, the reactions for formation of formaldehyde adducts seem to be nonenzymatic. They occur simply without the intervention of an enzyme to speed it up, and these are rapid equilibrium processes. Therefore, the only thing that might change is that you might have one form that is possibly a little bit more reactive than the others but in terms of being available at some point to the genome, to the DNA, certainly things would be available by equilibrium displacement.

Mr. CLEMENT. Dr. Clay, a final point for you: As a career employee and as a technical employee of the agency, at any time did you or the people below you in your department feel that formaldehyde was appropriately addressed for nomination under section 4(f) of TSCA?

Mr. CLAY. I certainly never felt so. We never had a vote of my staff people. I would think that some might have thought that, some might not have thought that, but I cannot speak for all of them. I have never asked them.

Mr. **Clement**. Is it correct that the first iteration under the 4(f) drill that you went through came up with a recommendation that formaldehyde be subjected to a 2-year data-gathering period to give you sufficient information to determine whether or not it should be regulated?

Mr. **Clay**. That was prior to my entry on board which took place in early August, but that is my understanding.

Mr. **Gore**. Well, if the gentleman would yield, didn't it also recommend that it be classified under 4(f)?

Mr. **Clay**. Again, it is before I got there. It was my understanding that the staff recommendation was to call it a 4(f), and by that they meant to go out and get the 2-year exposure data.

Mr. **Gore**. However, they did recommend that it be classified 4(f)?

Mr. **Clay**. That is what I am told. I was not there.

Mr. **Clement**. Mr. Pedersen, I am not going to let you escape. You have been sitting there very patiently. You are from the Office of General Counsel?

Mr. **Pedersen**. I am.

Mr. **Clement**. As one lawyer to another, let me ask you, is it at all appropriate in any circumstance to nominate a chemical as 4(f) and not regulate it but to subject it to a 2-year testing period?

Mr. **Pedersen**. Well, by happenstance I was about to speak to that point because my understanding is, the difference between the 4(f) recommendation and the non-4(f) recommendation is not a difference in what is to be done but in what you call it. In both cases the recommendation was the same, for a 2-year study of exposure. The question is, Is that a satisfactory response to the commands of section 4(f) or is it not? We think it is not because section 4(f) says that at the end of 180 days the agency must be ready to initiate action under one of the substantive regulatory provisions of TSCA or else it must find that there is not an unreasonable risk present, which means that it can scratch the chemical off its regulatory agenda. As I understand it, EPA knows quite well that it will not be in a position to do either of those things even if it should start the 4(f) clock. In those circumstances, we should not start the clock.

Mr. **Clement**. Therefore, it is the opinion of the General Counsel that under TSCA in this particular instance the action taken not to name formaldehyde as a 4(f) chemical is the correct action?

Mr. **Pedersen**. That is correct.

Mr. **Clement**. I have no further questions, Mr. Chairman.

Mr. **Gore**. The General Counsel is a career position?

Mr. **Pedersen**. The General Counsel is not a career position.

Mr. **Gore**. The General Counsel is appointed by Ms. Gorsuch?

Mr. **Pedersen**. Yes.

Dr. **Todhunter**. Mr. Pedersen is a career employee, however.

Mr. **Pedersen**. Yes.

Mr. **Gore**. Mr. Clay, you said you were a career employee. Do you feel comfortable with the scientific judgments and statements made by Dr. Todhunter in his February 10 memorandum?

Mr. **Clay**. As we have pointed out, I am an engineer, not a scientist.

Mr. **Gore**. Does your scientific staff feel comfortable with those judgments and statements?

Mr. **Clay**. To the best of my knowledge they do.

Mr. **Gore**. Well, I will not put you on the spot, Mr. Clay, but there are indications that members of the scientific staff do not agree with the statements made. Aren't there such indications?

Mr. **Clay**. Is that a question, sir?

Mr. **Gore**. Yes.

Mr. **Clay**. It is my understanding that a lot of what Dr. Todhunter has proposed is his professional judgment and one thing I have found, being around toxicologists and biochemists for a long time, is that they always disagree.

Mr. **Gore**. All right.

Dr. Todhunter, would you be willing to answer additional questions for the record? We do not anticipate a lengthy list.

Mr. **Gore**. Thank you very much.

That will conclude our questions for you and your colleagues. Thank you very much for coming here today.

Dr. **Todhunter**. Thank you for the opportunity to present our statement.

Mr. **Gore**. Our next panel is made up of Mr. Richard Dailey, a former employee of EPA, Dr. Frederica Perera, staff scientist with the Natural Resources Defense Council, and Ms. Jacqueline Warren, senior staff attorney with the Natural Resources Defense Council. Would the three of you come to the witness table?

Would you stand and be sworn, please? Raise your right hands and repeat after me: Do you swear that the testimony you are about to give will be the truth, the whole truth, and nothing but the truth, so help you God?

Mr. **Dailey**. I do.

Ms. **Warren**. I do.

Dr. **Perera**. I do.

Mr. **Gore**. Thank you very much.

Without objection, your prepared statements will be included in the record in full at the appropriate point. If you care to summarize, that will be fine with us. If you wish to read, that is OK, too. We will start with you, Mr. Dailey. Welcome. Thank you for being here.

Mr. **Dailey**. I would just prefer to read straight from my submitted testimony.

Mr. **Gore**. All right. Let me say that as a former employee of the agency, we realize that you have some difficulty coming here and we appreciate the fact that you are here at our specific request. Thank you very much. Go ahead with your statement.

## STATEMENT OF RICHARD L. DAILEY, FORMER EMPLOYEE OF THE ENVIRONMENTAL PROTECTION AGENCY

Mr. **Dailey**. As I begin my testimony today, I would ask that the members of the subcommittee bear two things in mind: First, I am not appearing here today as an expert on chemical carcinogenesis, analytical monitoring methods, epidemiology, or any of the other disciplines which when taken as a whole, lay the groundwork for an estimate of the human health risks posed by a given chemical.

It was my job at EPA, for want of a better word, to be a generalist. That is to say, I was to read, analyze, interpret, and synthesize scientific information made available to me and to provide management with accurate, succinct reports on whatever chemical was under consideration.

Second, I did not volunteer information on the formaldehyde issue to members of the investigation team of this subcommittee. I was called several times by the investigators and agreed to meet and discuss my role and recollections of EPA's handling of formaldehyde rather reluctantly. I was also extremely reluctant to testify before this subcommittee, and am doing so now only after receiving a letter from Representative Gore ordering me to do so.

EPA's involvement with formaldehyde began more than 2½ years ago. My professional responsibilities for handling the Agency's formaldehyde efforts extend back almost as far.

In October of 1979 the Agency received information submitted under section 8(e) of the Toxic Substances Control Act from Monsanto and Celanese Corp., indicating that several rats exposed to formaldehyde in a study undertaken by the Chemical Industry Institute of Toxicology, CIIT, had developed grossly observable tumors in the nasal area. These animals were, I believe, sacrificed in the 15th month of the study, although they may have died spontaneously. Subsequent histopathological preparations of transverse sections of the nasal turbinates revealed that the animals had developed nasal squamous epithelial carcinomas of the turbinates, a very rare type of tumor in the strain of rats—which were Fisher 344's—used in the study.

In December 1979 I was assigned to represent EPA on an interagency regulatory liaison group on formaldehyde. The significance of the widespread governmental interest in formaldehyde was evidenced by the fact that this IRLG group, in addition to the five member agencies, also included the Department of Energy and the Department of Housing and Urban Development.

In January 1980, CIIT carried out their scheduled 18-month sacrifice of exposed and control rats and mice. Information released by CIIT disclosed that the total number of nasal carcinomas found in scheduled and unscheduled animals had risen to 37. This significant increase in cancer in the high-dose rat group—15 parts per million—prompted the IRLG work group to sponsor an independent team of pathologists to review the CIIT histological preparations. In a short report to the IRLS work group, the pathologists confirmed the CIIT findings.

In March 1980, the Consumer Products Safety Commission assembled a group of expert scientists to form the Federal Panel on Formaldehyde, which operated under the auspices of the National Toxicology Program. At approximately the same time, which was March 1980, the regulatory development work group of the IRLG, under a directive from the heads of the respective IRLG agencies, charged the formaldehyde work group with the task of developing an integrated risk assessment on formaldehyde.

A pilot project, the regulatory development work group intended that this one document would serve as a working technical risk assessment that would provide sufficient technical information to cover all of the regulatory responsibilities and statutory mandates of the IRLG agencies plus DOE and HUD. An outline of the risk assessment and a work plan listing each participating agency's responsibilities and timetable was approved by the work group, and actual work was begun on the project around August 1980.

Also around March 1980, EPA placed formaldehyde on what was called the phase 1 queue of chemicals. Chemicals in the phase 1 queue, by virtue of their general toxicity, production volume, uses, and potential for human exposure, were considered by the Agency to pose sufficient threat to human health to warrant an extensive literature review, analysis, and quantitative risk assessment. However, in the interest of reducing duplication of effort, instead of initiating our own effort EPA contributed information, staff, and physical resources to the IRLG risk assessment effort.

During the time that the IRLG began working on its joint risk assessment, the aforementioned Federal Panel on Formaldehyde was completing its report. In November 1980 the panel made its report to CPSC, stating in a transmittal letter to Commissioner King that "formaldehyde should be presumed to pose a cancer risk to humans."

It was this report by the Federal Panel that prompted EPA to consider possible action on formaldehyde under section 4(f) of TSCA. The top officials of the Office of Toxic Substances believed that the report, which concluded that formaldehyde was carcinogenic in rats, constituted "receipt of information by the Administrator that a substance is carcinogenic." That is one of the criteria for initiating a 4(f) action. Receipt of this information, under the requirements of section 4(f), gave the Administrator 180 days to publish in the Federal Register what action the Agency would take or why no action was necessary.

The Agency was also in receipt of a formaldehyde exposure assessment which had been prepared for the IRLG risk assessment, which indicated the potential for widespread human exposure to formaldehyde. Examining these two documents, the Office of Toxic Substances determined that formaldehyde may pose "a serious risk of widespread harm for cancer," and thus may be a candidate for action under section 4(f).

In January 1981, the Office of Toxic Substances began work on a report called the "Priority Review Level 1," or the PRL-1, as we have all called it today. The PRL-1 would be used as a technical decision document by the Assistant Administrator for Toxic Substances in making his recommendation to the Administrator on the applicability of formaldehyde to section 4(f) and as to what action the agency should take. Because the office believed it was working against the 180-day time clock begun in November, the PRL-1 was to be completed in less than a month.

To accomplish this, EPA's Exposure Evaluation Division—which is also the Office of Toxic Substances—revised the exposure assessment that had been prepared for the IRLG risk assessment. This revised report was used as the PRL-1 chapter on exposure. EPA's Assessment Division, which had the lead responsibility for preparation of the PRL-1, used—with some minor modifications—the Federal Formaldehyde Panel's report for the PRL-1 chapters on metabolism and carcinogenicity. EPA's Health and Environmental Review Division, using exposure levels and population sizes from the exposure chapters and animal data from the CIIT study, used Dr. Crump's linearized multistage carncinogenisis model with upper 95 percent confidence limits to project cancer risks to various identified subpopulations.

The completed report was distributed throughout OTS for review and in March 1981, a disposition meeting was held whose attendees included the Deputy Assistant Administrator for Toxic Substances, Office of Toxic Substances division directors, and appropriate staff, as well as representatives of the agency's Office of General Counsel. It was decided at that meeting that formaldehyde met the section 4(f) cancer criterion, and that the exposure assessment chapter indicated that there would be sufficient potential for human exposure to formaldehyde. These two criteria, when taken together, satisfied the requirement for serious and widespread harm as stated in section 4(f) TSCA, and that it should be recommended to the Administrator that action should be taken on formaldehyde under section 4(f).

The Chemical Control Division of the Office of Toxic Substances then prepared several documents to send to Administrator Gorsuch. I was not directly involved with the preparation of these documents and therefore do not want to testify about those.

During the summer of 1981, a series of three meetings were called by newly appointed Deputy Administrator Hernandez to discuss the basic science behind formaldehyde's potential carcinogenicity, human exposure, completed epidemiological studies, and quantitative risk assessment. Attending these meetings were representatives of the Formaldehyde Institute, CIIT, and EPA staff. Several invited guests appeared at each of the three different meetings. However, several scientists from CPSC and OSHA, all of whom had extensive knowledge on the carcinogenic and epidemiologic aspects of formaldehyde, asked for and were denied permission to attend the meetings.

In September 1981, the newly appointed Director of the Office of Toxic Substances, Mr. Don Clay, requested EPA staff to prepare an options paper on formaldehyde that would help him make his recommendation to the new Assistant Administrator for Pesticides and Toxic Substances, Dr. John Todhunter. After considering the staff's options paper, Director Clay sent a memorandum to Dr. Todhunter recommending that section 4(f) not be applied to formaldehyde for three basic reasons.

They were, one, that the data used in the exposure assessment were not of sufficient quality; two, that completed epidemiological studies indicated that formaldehyde was probably not a human carcinogen, and that anyway the National Cancer Institute and the Formaldehyde Institute were conducting an epidemiology study which within 3 years should provide a better indication of formaldehyde's potential for human carcinogenicity; and, three, that there were as of yet unanswered questions as to the mechanisms of formaldehyde carcinogenesis in the rats in the CIIT study.

In October 1981 I was given a copy of the PRL-1 with changes to be made that had been penciled in by Dr. Todhunter. I questioned some of the changes that were to be made but was ordered to incorporate Dr. Todhunter's comments verbatim. One particular example stands out as illustrative of my reluctance to make the requested revisions.

During the course of the science court hearings held by Dr. Hernandez, Drs. Hernandez and Todhunter had emphatically stated that for the agency to maintain scientific credibility, staff scientists in preparing technical documents should adhere to the traditional demands of scientific rigor. They implied that only under special circumstances should data that has not received traditional peer review be used.

However, at one of the science court meetings, Dr. Hech, a researcher from CIIT, indicated that preliminary results from his work indicated that 3 ppm formaldehyde could be found in the nasal mucosa of unexposed rats. Dr. Hech implied that this was free formaldehyde. During a break in the meeting I asked Dr. Hech if it was not, in fact, more likely that formaldehyde was found as an adduct to tetrahydrofolate or glutathione and therefore unavailable for interaction with any cellular constituents. He stated that this was probably true, and we apprised Dr. Hernandez of this fact.

One of Dr. Todhunter's revisions in the PRL, however, stated that up to 3 ppm endogenous formaldehyde had been found in the nasal mucosa of rats not exposed to formaldehyde, citing Dr. Hech, 1981. He stated that one could conjecture, then, that 3 ppm could be a threshold below which one would not expect cancer induction.

I then called Dr. Hech at CIIT and asked if, since Dr. Todhunter's reference was of the type typically used for published literature, his paper on endogenous formaldehyde had been published. He replied no, and that it was not even in proper form to be sent to a journal for consideration. I then asked if anybody at the agency was in receipt of any personal communication from him stating the results of his findings. He answered negatively to that question, also. I then asked him, in his best estimate, how much of the endogenous formaldehyde—3 ppm—that he had mentioned to Dr. Hernandez would actually be found as free formaldehyde. He replied that at least 90 percent, in his best estimate, at least 90 percent would be bound as adducts.

I felt at that time that I could not in good conscience and without compromising my own integrity make the requested changes. I was then taken off the formaldehyde project for approximately 3 months. During that time, several versions of the document were developed by different staff. I do not have very much knowledge of what was included in those documents. In January 1982 I was asked to take responsibility for the formaldehyde project once more and was asked to make still more revisions in what as now, rather than being called the PRL-1, a "Technical Document on Formaldehyde." I was also asked to manage what was to be our continuing investigation into formaldehyde exposure and health problems.

A meeting was held between OTS division directors and appropriate staff to determine how to revise the document. It was decided at this meeting that our exposure data were too weak, that there were too many unanswered questions concerning the mechanisms of carcinogenesis resulting from the 15 ppm dose level in the CIIT experiment, and that therefore we could not even attempt to do quantitative risk assessment. Although I personally did not believe this to be true, I revised the document as instructed.

The document was returned several days later with handwritten comments from Dr. Todhunter ordering more changes. It was at this point that I tendered my resignation. I believe that it is the responsibility of a Government employee to carry out the objectives of his respective agency to the best of his ability, regardless of his personal position on those objectives. However, I also believe that when objectives and means of obtaining those objectives become so untenable as to compromise the quality of one's work and integrity, it is one's responsibility to resign that position, and that is what I have done.

Thank you.

[The prepared statement of Dr. Dailey follows:]

## STATEMENT OF RICHARD L. DAILEY

May 20, 1982

As I begin my testimony today, I would ask that the distinguished members of the Subcommittee bear two things in mind. First, I am not appearing here today as an expert on chemical carcinogenesis, analytical monitoring methods, epidemiology or any of the other disciplines which, when taken as a whole, lay the groundwork for an estimate of human health risks posed by a given chemical. It was my job at EPA to be, for want of a better word, a "generalist." That is to say, I was to read, analyze, interpret and synthesize scientific information made available to me, and to provide management with accurate, succinct reports on whatever chemical was under consideration.

Second, I did not volunteer information on the formaldehyde issue to members of the investigation team of this subcommittee. I was called several times by the investigators and agreed to meet and discuss my role and recollections in EPA's handling of formaldehyde rather reluctantly. I was also extremely reluctant to testify before this committee, and am doing so now only after receiving a letter from Representative Gore ordering me to do so.

EPA's involvement with formaldehyde began more than 2½ years ago. My professional responsibilities for handling the Agency's formaldehyde efforts extend back almost as far. In October of 1979, the Agency received information submitted under Section 8(e) of the Toxic Substances Control Act (TSCA) from Monsanto and Celanese indicating that several rats exposed to formaldehyde in a study undertaken by the Chemical Industry Institute of Toxicology (CIIT) had developed grossly observable tumors in the nasal area. These animals were, I believe, sacrificed at the 15th month of the study (although they may have died spontaneously.)

Histopathological preparations of transverse sections of the nasal turbinates revealed that the animals had developed nasal squamous epithelial cell carcinomas of the turbinates, a very rare type of tumor in the strain of rats, Fisher 344's, used in the study. In December of 1979 I was assigned to represent EPA on an Inter Agency Regulatory Liaison Group (IRLG) on Formaldehyde. The significance of the widespread governmental interest in formaldehyde was evidenced by this IRLG group in that, in addition to the five member agencies, the Department of Energy (DOE) and the Department of Housing and Urban Development (HUD) were also represented.

In January of 1980, CIIT carried out their scheduled 18 month sacrifice of exposed and control rats and mice. Information released by CIIT disclosed that the total number of nasal carcinomas found in scheduled and unscheduled animals had risen to 37. This significant increase in cancer in the high dose rat group (15 ppm) prompted the IRLG workgroup to sponsor an independent team of pathologists to review the CIIT histological preparations. In a short report to the IRLG workgroup, the pathologists confirmed the CIIT findings.

During March of 1980, the Consumer Product Safety Commission (CPSC) assembled a group of scientists to form the Federal Panel on Formaldehyde, which operated under the auspices of the National Toxicology Program. The charge to the panel was as follows:

> "The recent test results form the CIIT formaldehyde study for the 18 month sacrifice indicate that inhalation of 15 ppm of formaldehyde causes squamous cell carcinomas of the nasal cavity in rats. These findings have been confirmed by 6 pathologists participating in an IRLG review of this study. This panel is being formed for the purpose of determining the applicability of these data to the human situation. Within this context there would appear to be a number of questions to be answered about the CIIT study itself and then a variety of factors to be considered with regard to possible human carcinogenicity.
>
> Beginning with the CIIT study, the following questions would appear relevant:
>
> a. Is there evidence indicating that formaldehyde may be tumorgenic/carcinogenic at doses other than 15 ppm?
> b. Are there confounding factors in the CIIT study such as the irritating properties of formaldehyde, the viral infection, special susceptibility of the rat to irritants or protocol defects. If so, what are the relevant merits of these factors?

c. What conclusions can be arrived at with regard to tumorgenic/carcinogenic in the CIIT study?

In addition to the above, the following questions on potential human carcinogenicity would appear relevant:

a. What is the applicability of the conclusions in section (c), above, to the human situation?
b. If it is determined that the CIIT data are applicable to humans, then what are the confounding factors and how do they impact in the human situation? For example, what is our experience in relating animal data from other irritant carcinogens to the human situation? How do other formaldehyde studies in animals and epidemiological studies affect conclusions about the human carcinogenicity of formaldehyde? Do short term mutagenicity data support findings of carcinogenicity?
c. What conclusions can be reached with regard to the human carcinogenicity of formaldehyde and are there conditions to these conclusions?
d. Are there additional data needed?
e. Are these findings relevant to exposure from other routes?"

At approximately the same time (March 1980), the Regulatory Development Workgroup (RDWG) of the IRLG, under orders from the heads of the respective IRLG Agencies, charged the Formaldehyde Workgroup with the task of developing an "integrated" risk assessment on formaldehyde. A pilot project, the RDWG intended that this one document would serve as a working, technical risk assessment that would provide sufficient technical information to cover all of the regulatory responsibilities and statutory mandates of the IRLG agencies plus DOE and HUD. An outline for the risk assessment and a workplan listing each participating agency's responsibilities and timetable was approved by the workgroup, and actual work was begun on the project around August 1980.

Also around March of 1980, EPA placed formaldehyde on the Phase 1 queue of chemicals. Chemicals in the Phase I queue, by virtue of their general toxicity, production volume, uses and potential for human exposure, were considered by the Agency to pose sufficient threat to human health to warrant an extensive literature review, analysis, and qualitative risk assessment. However, in the interest of reducing duplication of effort, instead of initiating an effort of its own, EPA contributed information, staff and fiscal resources to the IRLG risk assessment effort.

During the time that the IRLG began working on its joint risk assessment, the aforementioned Federal Panel on Formaldehyde was completing its report. In November of 1980, the Panel made its report to CPSC, stating in a transmittal letter to Commissioner King that "formaldehyde should be presumed to pose a cancer risk to humans."

It was this report by the Federal Panel that prompted EPA to consider possible action on formaldehyde under Section 4(f) of TSCA. The top officials of the Office of Toxic Substances believed that the report, which concluded that formaldehyde was carcinogenic in rats, constituted "receipt of information by the Administrator that a substance is carcinogenic" that is one of the criteria for initiating 4(f) action. Receipt of this information, under the requirements of Sec. 4(f) gave the Administrator 180 days to publish in the Federal Register what action the Agency would take, or why no action was necessary.

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To accomplish this, EPA's Exposure Evaluation Division (EED) revised the exposure assessment prepared for the IRLG risk assessment. This revised report was used as the PRL-I chapter on exposure. EPA's Assessment Division, which had the lead responsibility for the preparation of the PRL-I, used,, with some minor modifications, the Federal Panel's report for the PRL-I chapters on metabolism and carcinogenicity. EPA's Health and Environmental Review Division using exposure levels and population sizes from the exposure chapters, animal data from the CIIT study, used Dr. Crump's linearized multi-stage carcinogenisis model with upper 95% confidence limits to project cancer risks to various identified sub-populations.

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The Chemical Control Division of OTS then prepared several documents to send to Administrator Gorsuch. I was not directly involved with the preparation of these documents.

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I felt at that time, that I could not, in good conscience and without compromising my own integrity, make the requested changes. I was taken off the formaldehyde project, for approximately three months. During that time several versions of the document were developed by different staff. In January of 1982

I was asked to make still more revisions to what was now called a "Technical Document on Formaldehyde," and to manage what was to be our continuing investigation into formaldehyde exposure and health problems.

A meeting was held between OTS Division Directors and appropriate staff to determine how to revise the document. It was decided at this meeting that our exposure data were too weak, that there were too many unanswered questions concerning the mechanism of carcinogenesis resulting from the 15 ppm dose level in the CIIT experiment, and that, therefore, we could not even attempt to do quantitative risk assessment. Although I personally did not believe this to be true, I revised the document as instructed. The document was returned several days later with handwritten comments from Dr. Todhunter ordering more changes.

It was at this point that I tendered my resignation. I believe that it is the responsibility of a government employee to carry out the objectives of his respective agency to the best of his ability, regardless of his personal position on those objectives. However, I also believe that when objectives and means of obtaining those objectives become so untenable as to compromise the quality of one's work and integrity, it is one's responsibility to resign that position. That is what I have done.

Mr. **Gore**. Well, thank you very much. I am glad we insisted that you come here. That is a very important statement.

Dr. Perera?

## STATEMENT OF DR. FREDERICA P. PERERA, SENIOR STAFF SCIENTIST, NATURAL RESOURCES DEFENSE COUNCIL, INC.

Dr. **Perera**. My name is Frederica Perera. I hold a doctorate in public health and I am a senior staff scientist with the Natural Resources Defense Council. NRDC is a national public interest environmental organization with more than 40,000 members. One of NRDC's major interests is the adequate protection of public health against toxic chemicals in the environment.

EPA's current position regarding formaldehyde, as expressed by Dr. Todhunter, is that data now available do not indicate that formaldehyde presents or will present a significant risk to human health. We disagree with this conclusion. We are concerned about the health hazard of formaldehyde itself, and about the significance of this decision in terms of EPA's overall policy concerning public health protection against carcinogenic substances.

First, formaldehyde is a high-volume chemical with an approximate annual production of 7 billion pounds. An estimated 1.5 million workers are exposed to formaldehyde. Millions of people may breathe formaldehyde vapors in the home, released by construction and insulation materials. Formaldehyde is found in polluted air and in a great many consumer products such as permanent-press fabrics, preservatives used in school and hospital laboratories, drugs, and cosmetics.

According to the reports of the National Toxicology Panel [NTP] and the Mount Sinai School of Medicine environmental cancer information unit, headed by Dr. Richard Griesemer and Dr. Irving Selikoff, respectively, the levels encountered by humans in some workplace and home environments are comparable to those that cause tumors in the animals. The CIIT data showing formaldehyde to produce tumors in animals have been judged to be valid by NTP, Mount Sinai, and the IARC, as well as by many other distinguished scientists. The findings of the CIIT study are confirmed by the results of the NYU study soon to be published in the "Journal of the National Cancer Institute."

Their review of all the experimental data, consistent with established policy for assessing the risks of carcinogens, has led NTP, Mt. Sinai, IARC, and other scientists, including the directors of major U.S. research institutes, to conclude that formaldehyde gas should be considered "for practical purposes" as if it represented a risk of cancer to humans. These scientists include Dr. Arthur Upton, Dr. Norton Nelson, and Dr. Roy Albert of NYU; Dr. Vincent de Vita, Director, NCI; Dr. J. D. Millar, Director, NIOSH; Dr. David Rall, Director, NTP and NIEHS; Dr. Ronald Hart, Director, NCTR; Dr. Bernard Weinstein of Columbia University; and Dr. Sidney Weinhouse of the Fells Research Institute.

Based on the Mount Sinai report, in February 1982, the American Cancer Society issued a public statement urging regulatory agencies to set appropriate standards to minimize human exposure to formaldehyde. This statement echoed an earlier recommendation to the heads of EPA, OSHA, and CPSC by Dr. Upton of New York University, and Dr. I. B. Weinstein of Columbia University, that these agencies take prudent measures to restrict human exposures to formaldehyde.

Therefore, the statements by Dr. Todhunter that formaldehyde is "a potential animal" human carcinogen, on page 8 of his memo, and that "concern that formaldehyde gas may induce tumors in humans may be tempered" by the observation of "species specificity and a strong dependence on route of exposure," page 7, stand in sharp contrast with the prior judgments of experts in carcinogenesis.

As you have also heard from previous speakers, the discussion in the Todhunter memo concerning the likelihood that formaldehyde produces tumors via an indirect mechanism of action, with the result that there is probably a threshold for the carcinogenic effect, likewise contradicts other assessments including those by NTP, Mount Sinai, CPSC's health science staff, and EPA's Office of Toxic Substances (1981). For example, CPSC scientists have recently reviewed the various "threshold" arguments and have reaffirmed their earlier conclusion that there is no evidence for a threshold for the carcinogenic effect of formaldehyde. Any exposure to formaldehyde can thus be assumed to pose some additional risk of cancer.

According to IARC, the available epidemiological data on formaldehyde are "inadequate" to evaluate the carcinogenic effect in human populations. Because of various shortcomings of epidemiological studies conducted to date—such as too few people studied, poor documentation of exposure, failure to take into account the lag between exposure and appearance of tumors, et cetera—the NTP, NIOSH, EPA's OTS (1981), and CPSC staff have termed the studies "inconclusive" but not negative. However, Dr. Aaron Blair of the NCI has noted that the preliminary epidemiological findings suggest an increased risk of cancer at different sites in workers.

As Dr. Nelson has noted in his written testimony, recent preliminary reports of nasal cancers in workers, if confirmed, could provide decisive evidence of an association.

The sole conclusion, consistent with the judgments of experts in carcinogenesis and with accepted policy concerning assessment of carcinogenic risk, is the following: In the absence of adequate epidemiological data, and on the basis of the animal studies, formaldehyde should be considered to pose a risk of cancer to humans. Accordingly, appropriate and necessary steps should be taken by EPA, as have been taken by CPSC, to reduce human exposure.

In our view, the EPA decision on formaldehyde may constitute an ad hoc revision of the principles for assessing carcinogenic risk that have been widely accepted by the scientific community for over a decade. These principles have been elaborated in several dozen reports by international and national scientific committees during the past 10 years, and underlie present Federal policies for the identification and assessment of potential human carcinogens.

In his testimony this morning, Dr. Nelson has explained the basis for these principles, which I will not reiterate. The principles have been recently reexamined and confirmed by the Office of Technology Assessment report entitled "Assessment of Technologies for Determining Cancer Risks From the Environment." I will simply summarize, noting that my written testimony has additional explanation. They are as follows:

1. Animal testing data from properly designed and well conducted tests are adequate for concluding that a chemical substance or agent is a likely carcinogen in humans.

2. It is not currently possible, using available methods, to extrapolate from animal data a safe population threshold for any carcinogen, regardless of the mechanism of action. I will just add one sentence of explanation: Even in those cases where it was possible to determine with absolute certainty experimental thresholds and the mechanism by which a substance or agent induces tumors, it would not now be possible to identify a safe level of exposure for the human population. This is because of the variation in human host response and the multiplicity of human exposures to carcinogens.

3. The third principle is that positive human data are not necessary to regard an agent as a likely human carcinogen warranting protective action. Accordingly, Federal agencies have regulated such substances as hair dyes, pesticides, food additives, and industrial carcinogens solely or principally on the basis of results in animal tests.

For all these reasons, EPA's decision not to make formaldehyde a priority for regulatory assessment on the basis of the arguments presented in the Todhunter memo could effectively rewrite the agency's cancer policy. The result would be a significant relaxation of public health protection from cancer-causing substances. We believe that there is a consensus in the scientific community that there are no new data which would justify such a serious departure from the major principles of established cancer policy.

Dr. Upton and Dr. Weinstein have written: "It has come to our attention that EPA, OSHA, and possibly other Federal regulatory agencies, may be planning not to take immediate protective action on formaldehyde, in spite of substantial evidence for its carcinogenicity from animal bioassays. We are concerned about the possibility of such a departure from established public health policy. It would conflict with the prevailing views of the scientific community and would set a precedent which could hamper future regulatory action on other carcinogens."

Thank you.

[The prepared statement of Dr. Perera follows:]

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# TESTIMONY OF

## FREDERICA P. PERERA, Dr. P.H.

NATURAL RESOURCES DEFENSE COUNCIL

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

OF THE

U.S. HOUSE OF REPRESENTATIVES

COMMITTEE ON SCIENCE AND TECHNOLOGY

May 20, 1983

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My name is Frederica Perera. I am a Senior Staff Scientist with the Natural Resources Defense Council (NRDC). NRDC is a national public interest environmental organization with more than 40,000 members. One of NRDC's major interests is the adequate protection of public health against toxic chemicals in the environment.

EPA's current position regarding formaldehyde as expressed by Dr. Todhunter in a February 10, 1982 memorandum to EPA Administrator Gorsuch is that data now available do not indicate that formaldehyde presents or will present a significant risk to human health.[1] NRDC disagrees with this conclusion. We are concerned about the health hazard of formaldehyde itself and about the significance of this decision in terms of EPA's overall policy concerning public health protection against carcinogenic substances.

First, formaldehyde is a high-volume chemical with an approximate annual production of seven billion pounds. An estimated one and a half million workers are exposed to formaldehyde; another eleven million people may breathe formaldehyde vapors in the home, released by construction and insulation materials.[2] Formaldehyde is found in polluted air and in a great many consumer products such as permanent press fabrics, preservatives used in school and hospital laboratories, drugs and cosmetics.

According to the reports of the National Toxicology Program (NTP) panel and the Mt. Sinai School of Medicine Environmental Cancer Information Unit, headed by Dr. Richard Griesemer and Dr. Irving Selikoff respectively, the levels encountered by humans in some workplace and home environments are comparable to those that caused tumors in animals.[3,4]

The Chemical Industry Institute of Toxicology (CIIT) data showing formaldehyde to produce tumors in animals have been judged to be valid by NTP,[3] Mt. Sinai School of Medicine Environmental Cancer Information Unit,[4] and the International Agency for Research on Cancer (IARC)[5] as well as by many other distinguished scientists.[6] The findings of the CIIT study are confirmed by the results of the NYU studies soon to be published in the Journal of the National Cancer Institute.[7]

Their review of the experimental data, consistent with established policy for assessing the risks of carcinogens, has led NTP, Mt. Sinai, IARC, and other scientists including the directors of major U.S. research institutes to conclude that formaldehyde gas should be considered "for practical purposes" as if it represented a risk of cancer to humans. These scientists include Dr. Arthur Upton, Dr. Norton Nelson, and Dr. Roy Albert of New York University; Dr. Vincent de Vita, Director, National Cancer Institute (NCI); Dr. J. D. Millar, Director, National

Institute of Occupational Safety and Health (NIOSH); Dr. David Rall, Director, NTP and National Institute of Environmental Health Sciences; Dr. Ronald Hart, Director, National Center for Toxicological Research; and Dr. I. B. Weinstein of Columbia University.[6,8]

Based on the Mt. Sinai Report in February 1982, the American Cancer Society issued a public statement urging regulatory agencies to set appropriate standards to minimize human exposure to formaldehyde. This statement echoed an earlier recommendation to the heads of EPA, OSHA, and CPSC by Dr. Arthur Upton of New York University and Dr. I. B. Weinstein of Columbia University that these agencies take prudent measures to restrict human exposures to formaldehyde.[8]

Therefore, the statements by Dr. Todhunter that formaldehyde is a "potential" animal carcinogen and that "concern that formaldehyde gas may induce tumors in humans may be tempered" by the observation of "species specificity and a strong dependence on route of exposure" (p. 7) stand in sharp contrast with the prior judgements of experts in carcinogenesis.

As you have also heard from previous speakers, the discussion in the Todhunter memo concerning the likelihood that formaldehyde produces tumors via an indirect mechanism of action, with the result that there is probably a threshold for the carcinogenic effect, likewise contradicts other assessments including those by NTP, Mt. Sinai, CPSC's health science staff[6,10] and EPA's Office of Toxic Substances (OTS) (1981). All of these reviews noted, as has Dr. Todhunter, that formaldehyde is capable of directly interacting with the genetic material. They rejected the view that the cytotoxic (causing injury to the cell) or irritant effect of formaldehyde was sufficient to induce tumors, was a necessary prerequisite, or was likely to have been the dominant factor in their production. CPSC scientists have recently reviewed the various "threshold" arguments prior to recommending a final ban on urea-formaldehyde foam insulation and have reaffirmed their earlier conclusion that there is no evidence for a threshold for the carcinogenic effect of formaldehyde.[6,10] Any exposure to formaldehyde can thus be assumed to pose some additional risk of cancer.

Therefore, the observation by Dr. Todhunter that tumors appear to be secondary to cell injury triggered only at high levels of exposure ("simply put, the animals developed open sores in their nasal tissues after which tumors appeared") is contrary to these expert reviews.

According to IARC, the available epidemiological data on formaldehyde are "inadequate" to evaluate the cancer-causing effect in human populations.[5] Because of various shortcomings of epidemiological studies conducted to date (such as too few people studied, poor documentation of exposure, failure to take into account the lag between exposure and appearance of tumors, etc.) the NTP, NIOSH, EPA's OTS (1981) and CPSC staff have termed the studies "inconclusive" but not negative.[3,6,11,12] However, Dr. Aaron Blair of the NCI noted in a presentation to the National Cancer Advisory Board on October 5, 1981 that the preliminary epidemiological findings suggested an increased risk of cancer at different sites in workers.[13]

The sole conclusion consistent with the judgments of experts in carcinogenesis and with accepted policy concerning assessment of carcinoginic risk is the following: in the absence of adequate epidemiological data and on the basis of the animal studies, formaldehyde should be considered to pose a risk of cancer to humans. Accordingly, appropriate and necessary steps should be taken by EPA, as have been taken by CPSC, to reduce human exposure.

In our view, the EPA decision on formaldehyde may constitute an ad hoc revision of the principles for assessing carcinogenic risk that have been widely accepted by the scientific community for over a decade. These principles have been elaborated in several dozen reports by international and national scientific committees during the past ten years and underlie present federal policies for the identification and assessment of potential human carcinogens.[14] The reports include those of the National Cancer Advisory Board, the National Research Council, the

Interagency Regulatory Liasion Group, the Food Safety Council, the Office of Technology Assessment, the Occupational Safety and Health Administration, and the Toxic Substances Strategy Committee.[15]

The principles are as follows:

1. Animal testing data from properly designed and well conducted tests are adequate for concluding that a chemical substance or agent is a likely carcinogen in humans.

This principle rests on the broad scientific consensus that (a) testing at high-dose levels is a valid and necessary procedure for discovering possible carcinogenic hazards in man, and (b) because basic biological processes are generally similar from one mammalian species to another, results in laboratory animals selected as the most sensitive species (where this information is available) are qualitatively relevant to humans even though the site and type of tumor may differ.

2. It is not possible to extrapolate from animal data a "safe" population threshold for any carcinogen regardless of the mechanism of action.

There is general agreement that it is currently impossible to demonstrate a "risk-free" dose of a carcinogen for a group of diverse individuals regardless of the mechanism of action of the carcinogen.

Thus, even in those cases where it were possible to determine with absolute certainty experimental thresholds and the mechanism by which a substance or agent induces tumors, it would not now be possible to identify a safe level of exposure for the human population. In writing to federal officials about formaldehyde, Drs. Upton and Weinstein state: "There is no recognized method as yet for determining the existence of a threshold for a carcinogen in the human population."[9]

3. Positive human data are not necessary to regard an agent as a likely human carcinogen warranting protective action.

Epidemiological studies have limited ability to identify carcinogens due to factors such as cost, the long latency of cancer, the confounding effect of multiple exposures to carcinogens, and difficulties in identifying an appropriate control group. These factors can lead to the possibility of "false negative" results. Thus, although they may be useful in placing upper bounds on the magnitude of the risk, nonpositive epidemiological data do not deny the conclusion of carcinogenicity on the basis of animal assays.

In conclusion, according to a recent report by the Office of Technology Assessment, in 1981 all agencies accepted a "positive bioassay result in a single species as evidence that the substance is a potential human carcinogen," "do not accept the idea of thresholds in making decisions about carcinogenic risks," and believe that they should not wait for epidemiological evidence before taking action to limit human exposure to chemicals considered to be carcinogenic."[15] In fact, federal agencies have regulated such substances as hair dyes, pesticides, food additives, and industrial carcinogens solely or principally on the basis of results in animal tests.[16]

For all these reasons, EPA's decision not to make formaldehyde a priority for regulatory assessment on the basis of arguments presented in the Todhunter memo could effectively rewrite the Agency's cancer policy. The result could be a significant relaxation of public health protection from cancer-causing substances -- not only from formaldehyde but from other carcinogenic substances in our environment.

We believe that there is a consensus in the scientific community that there are no new data that would justify such a departure from the major principles of established cancer policy. Dr. Upton and Dr. Weinstein have written:

> "It has come to our attention that EPA, OSHA, and possibly other federal regulatory agencies, may be planning not to take immediate protective action on formaldehyde, in spite of substantial evidence for its carcinogenicity from animal bioassays. We are concerned about the possibility of such a departure from established public health policy. It would conflict with the prevailing views of the scientific community and would set a precedent which could hamper future regulatory action on other carcinogens."

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Mr. GORE. Thank you very much. Excellent testimony.

Ms. Warren? Without objection, your entire text will be put in the record at the appropriate point. Could you summarize your statement?

## STATEMENT OF JACQUELINE WARREN, SENIOR STAFF ATTORNEY, NATURAL RESOURCES DEFENSE COUNCIL

Ms. WARREN. Yes, I will. I would like to speak to our interpretation of what section 4(f) of TSCA is all about. Dr. Todhunter said in his testimony that it is not a regulatory vehicle, it is a priority setting mechanism, and that is absolutely correct. It was Congress' way of bringing to EPA's attention those chemicals which posed a risk of cancer, genetic mutations, or birth defects, so that they could have a higher priority for assessment and possible regulatory action than the myriad of other chemicals that EPA could address under TSCA. It just takes chemicals for which there is evidence of that kind and bumps them to the top of the list.

The fact that EPA now has underway some kind of a longer term assessment of formaldehyde, I do not think is coincidental. It is directly related to the fact that there was an EPA staff recommendation to designate this as a 4(f) chemical and a controversy surrounding that. But there is a serious question in my mind whether there would be anything going on formaldehyde at EPA today if it were not for the fact that the original conclusion by the EPA staff was that section 4(f) was triggered.

The period that is triggered by section 4(f) is a 6- to 9-month period during which information, which would be animal data plus some other evidence that might provide a reasonable basis for concluding that there is a significant risk, is subjected to close scrutiny, and a determination made whether regulatory action is appropriate or not. If all section 4(f) is, is something to require us to regulate when there is a very serious hazard, you do not need 4(f). You have sections 5, 6, and 7 for that already. Section 4(f) has to mean something different from that and the commonsense reading of it would be that when there may be a reasonable basis, that is not conclusive evidence; when there is enough evidence to think that there may be a basis for concluding that a substance poses a significant risk, EPA is given 6 to 9 months to look at it and decide whether it does or does not pose a significant risk. Then the Agency must initiate appropriate action.

I would like to point out one thing: There is a comparable section in TSCA, which is section 4(e). That section requires EPA, within the course of 1 year, to receive recommendations of high priority candidates for testing and make a decision whether to initiate the testing or not. EPA is given a whole year for this, and the statutory requirement is that they initiate rulemaking or publish a statement why testing is not necessary.

Section 4(f) by comparison does not use the words "initiate a rulemaking proceeding." It says "initiate appropriate action," and EPA has a lot of discretion in what it can do. They could put out an advance notice of proposed rulemaking to gather further information on exposure. With regard to formaldehyde, they could have required that some process changes be made to reduce the offgassing of formaldehyde from different products. The question of putting out a ban in 6 months I think is really not one that Congress had in mind. Clearly, you as Members of Congress know that it takes EPA 1 year to 2 years to put out a regulation. It takes 1 year to get the proposal in place, just in a form to go into the Federal Register. We and also the EPA's Office of General Counsel, in a published document called "Primer on Section 4(f)"—which if it is not in the record already, I would ask permission to supply to the committee to be put into the record—agree on the interpretation of section 4(f) that I am presenting to you, that it is a priority setting provision which does not require that a rule be proposed at the end of the 6- or 9-month period.

If that were necessary, it would not make any sense to have the 180 days start to run from the receipt of the information. If Dr. Todhunter's interpretation is correct, however, then EPA is not going to regulate very many chemicals or even have to look at very many chemicals under section 4(f). In our view the purpose of section 4(f) is to take a second, closer look at substances that raise serious red flags, and make a decision whether regulation is appropriate. If you have to wait until you have enough information to regulate before the section is even triggered, it seems to me that it is simply repetitive of the authority that is already in the statute.

We have already heard that the information on formaldehyde came in and that the EPA staff assessed it, assessed the NTP data, and the CIIT data, and made a recommendation that section 4(f) was triggered. Their recommendation was not for regulatory action. It never went into the Federal Register and so I do not know where recommendations were made for EPA to regulate. But earlier testimony, in fact, Dr. Todhunter's testimony, refers to misconceptions that EPA was going to regulate formaldehyde. I have not seen those recommendations so I do not know what Dr. Todhunter was referring to. That certainly did not come from us, although we have been some of the principal actors from the private, nonprofit environmental community urging that some action be taken with respect to formaldehyde.

After the recommendation was made to Mrs. Gorsuch that section 4(f) be triggered for formaldehyde, Dr. Hernandez held a series of secret science courts. That has been a subject of congressional hearings and I will not go into it here. But I would like to speak to the whole process that we have seen at EPA because in our view, not only have the scientific principles for assessing cancer risk been cast aside in favor of questionable and debatable threshold theories which leave the public at continuing risk, but the legal threshold for taking a closer look at potential carcinogens, mutagens, and teratogens has been raised to a level which few chemicals are likely to meet. Instead of a priority setting provision designed to force potentially very dangerous chemicals to EPA's immediate attention, section 4(f) has been transformed into a vehicle for addressing those "situations that require a crash effort to remedy a very serious hazard to public health." I am quoting now from Mr. Clay's September 11 memorandum. The basic congressional intent to require EPA on a expedited basis to take a closer look at chemicals that cause the most serious adverse effects in laboratory studies and for which there appears to be widespread exposure, has been completely frustrated. Apparently EPA is willing to take a second look only when a "very serious hazard to public health" has already been demonstrated. We submit to you that that is not the purpose of section 4(f), and expect to be engaged in litigation on the matter very shortly.

Although EPA did not make public until the Todhunter February 10 memorandum what its reason for not considering formaldehyde as a priority candidate under section 4(f) was, as early as November of 1981 the Agency staff was busy rewriting the PRL-1 document to support the reversal of policy. We have heard discussions of how that became the technical document, and that became the Todhunter memorandum, and I understand that you now have a copy of a March 10 document which is yet a further iteration. I am not quite sure what all of these documents are being prepared for but there was some indication from Mr. Clay earlier that some of it is in anticipation of our litigation, although it has the ring of ex post facto explanations for decisions made at a prior time.

I have included in my testimony some examples of the kinds of excisions, deletions, and insertions of other explanatory material EPA carried out, but the bottom line of it is that the PRL-1 document supported a recommendation to designate formaldehyde as a 4(f) chemical and begin to take appropriate action. The technical document and the Todhunter memorandum now have come to the reverse conclusion and they rely on reinterpretations of the same data to come to the opposite conclusion.

There are no new data to support the reversal, only a reinterpretation which has been advocated by and is quite favorable to the interests of the formaldehyde industry. Those new assumptions, as we have heard, depart radically from accepted principles of cancer risk assessment. They lack a sound scientific basis and leave the public subject to cancer risks that TSCA and the other regulatory statutes were designed to protect against. In our view, this has been an effort to get the Government off the back of the formaldehyde industry, and in this effort EPA has engaged in a series of actions that we consider procedurally improper, violative of the agency's statutory duty under section 4(f) of TSCA, and not in the public interest.

Thank you.

[The prepared statement of Dr. Warren follows:]

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TESTIMONY OF

JACQUELINE M. WARREN

NATURAL RESOURCES DEFENSE COUNCIL

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

OF THE

HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY

MAY 20, 1982

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Since the Natural Resources Defense Council (NRDC) was created in 1970, its staff attorneys and scientists have been involved in administrative, legal and legislative efforts to reduce involuntary exposures to toxic and especially cancer-causing substances in the environment. Among other statutes, NRDC has monitored the EPA's implementation of the Toxic Substances Control Act (TSCA) since its passage in 1976. TSCA was passed in response to repeated disclosures about the severe adverse health, environmental, and economic damage inflicted by such widely used substances as PCBs, kepone, vinyl chloride, PBBs and asbestos, to name but a few. The Act was intended to remedy the lack of legal authority to prevent such problems from arising, or to deal adequately with them after the fact of injury or serious risk was established.

In order to ensure that the potentially worst "bad actor" chemicals, i.e., those capable of causing cancer, genetic mutations or birth defects, would come to EPA's attention and be accorded a high priority for both assessment and possible regulatory action, Congress included §4(f) in TSCA. Section 4(f) provides that within 180 days of receipt of data indicating the possibility that a chemical poses a significant risk to humans of cancer, gene mutations or birth defects, the Administrator is required to initiate action to mitigate the risk under the regulatory sections of the Act, or else to publish a statement in the Federal Register explaining why the risk is not unreasonable.[1]

In November of 1980, EPA received information from the Chemical Industry Institute of Toxicology (CIIT) demonstrating that formaldehyde is carcinogenic in laboratory rats. Subsequently, the Agency received the report of a panel convened by the National Toxicology Program which reviewed and confirmed the findings of the CIIT study, and concluded that "formaldehyde should be presumed to pose a risk of cancer to humans."[2] This information, coupled with data demonstrating a possibly high level of human exposure to formaldehyde due to its widespread use in the workplace and home led the Agency staff to conclude and recommend formally that action was required under §4(f). The staff recommendation was supported by a lengthy document prepared by the Office of Toxic Substances, assessing the risks of formaldehyde exposure, entitled "Priority Review Level I (PRL-I)," dated February 19, 1981.

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[1] Section 4 (f), entitled "Required Action," provides: Upon the receipt of (1) any test data required to be submitted this Act, or (2) any other information available to the Administrator, which indicates to the Administrator that there may be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant risk of serious or widespread harm to human beings from cancer, gene mutuations, or birth defects, the Administrator shall, within the 180 day period beginning on the date of the receipt of such data or information, initiate appropriate action under §§5, 6, or 7 to prevent or reduce to a sufficient extent such risk or publish in the Federal Register a finding that such risk is not unreasonable. For good cause shown the Administrator may extend such period for an additional period of not more than 90 days. The Administrator shall publish in the Federal Register notice of any such extension and the reasons therefor. 15 U.S.C. §2603(f).

[2] R.A. Griesemer, A.G. Ulsamer, et. al., Report of the Federal Panel on Formaldehyde, November 1980.

A draft Federal Register Notice designating formaldehyde as a priority chemical under §4(f) was prepared for the new Administrator's signature in May 1981. The draft notice included the following statement:

> EPA believes that formaldehyde has met the criteria for §4(f) for the following reasons. First, the results of a recently reported bioassay study demonstrate that formaldehyde is carcinogenic in rats. A [NTP] panel, which evaluated the 18-month data, concluded that formaldehyde should be presumed to pose a risk of cancer to humans. EPA's evaluation of the 24-month results supports their conclusions. Second, review of the available information on the use of formaldehyde and resulting human exposure suggests that large numbers of people are potentially exposed to harmful concentrations of formaldehyde. Accordingly, the Agency finds that there may be a reasonable basis to conclude that formaldehyde presents a significant risk of widespread harm to humans from cancer.[1]

Instead of signing the notice acknowledging that §4(f) had been triggered and that priority assessment of formaldehyde as a potential candidate for regulation was underway, the Administrator turned the matter over to the Deputy Administrator, John Hernandez. Dr. Hernandez proceeded to conduct a series of secret "science courts" attended primarily by scientists and lawyers from the Formaldehyde Institute, the formaldehyde industry trade association, and EPA staff. Thereafter, on September 11, 1981, the EPA staff recommendation to designate formaldehyde as a §4(f) priority chemical was reversed.[1]

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[1] Formaldehyde Federal Register Notice at 5-6 (emphasis added).

The propriety of the "science courts" was the subject of a number of Congressional hearings in the fall of 1981 and will not be discussed further here. Suffice it to say that the Clay Memorandum appeared to reverse ten years of EPA and federal policy regarding the regulation of carcinogens. Adopting the Formaldehyde Institute's arguments, many of which have been put forth over the same period by other industry representatives in other proceedings involving regulation of exposures to carcinogens, the Clay Memorandum raised the threshold for action against carcinogenic chemicals so high that §4(f) is unlikely ever to be used.

As noted above, the purpose of §4(f) is to identify chemicals posing significant risks of cancer, birth defects or gene mutations in humans as high priority candidates for regulatory action, and to force the Agency to act quickly to mitigate these risks. By mandating that the Administrator take "appropriate regulatory action" under TSCA within 180 days with respect to chemicals posing such risks, §4(f) imposes a nondiscretionary duty to initiate expeditious action to mitigate those risks. Because as of last September, EPA had offered no explanation for its apparent decision not to designate formaldehyde as a §4(f) chemical, NRDC filed a 60-day letter noticing its intent to seek judicial review of the Agency's failure to comply with its statutory duty under §4(f). That suit has not yet been filed because from November 1981 to February 1982, a number of internal actions concerning formaldehyde appeared to be underway at EPA. It is now clear, however, that those actions were in the nature of attempts to revise the definition of risks warranting regulatory attention, and to rewrite the risk assessment documents for formaldehyde in order to support EPA's determination, following the secret "science courts," that formaldehyde does not pose a significant cancer risk to humans.

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[1] Memorandum from Office Director Don Clay to Assistant Administrator Designate John Todhunter, September 11, 1981 (hereinafter "Clay Memorandum").

Not only have the scientific principles for assessing cancer risk to humans been cast aside in favor of questionable "threshold" theories which leave the public at continuing risk, but the legal threshold for taking a closer look at potential carcinogens, mutagens and teratogens has been raised to a level which few chemicals are likely to meet. Instead of a priority-setting provision designed to force potentially very hazardous chemicals to EPA's immediate attention, §4(f) has been transformed into a vehicle for addressing "those situations that require a crash effort to remedy a very serious hazard to public health."[1] Since TSCA provides other authority for dealing with imminent hazards (§7) and chemicals found to pose unreasonable risks (§6), the latter interpretation of §4(f) effectively writes the provision out of TSCA. The basic Congressional intent to require EPA on an expedited basis to take a closer look at chemicals that cause the most serious adverse effects in laboratory studies, and for which there appears to be widespread exposure, is thereby completely frustrated. Instead, EPA is willing to take a second look at a chemical only when a "very serious hazard to public health" has already been demonstrated. Thus, EPA has rewritten both the science and the law in order to justify its failure to address formaldehyde under §4(f).[2]

Although EPA did not make public, until the Todhunter Memorandum in February 1982, its full explanation for deciding not to consider formaldehyde as a priority candidate for regulatory consideration under §4(f), as early as November 1981 Agency staff were engaged in re-writing the Priority Review Level I document to support the reversal of policy. A document dated November 16, 1981, entitled Technical Document on Formaldehyde, (TD), represents a highly selective revision of the original EPA risk assessment document which recommended 4(f) status for formaldehyde. In an apparent effort to alter the PRL-I document so as to support a recommendation *against* a 4(f) designation, key sentences were deleted from the text and new sections inserted generally without explanation or rationale. Moreover, relevant new information was not included. The overall effect of this editing and revision was to decrease the estimate of significance of the risk of exposure to formaldehyde. The following examples are illustrative of the changes made in the findings and conclusions of the PRL-I document. According to the PRL-I document,

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[1] Clay Memorandum at 3.

[2] It should be noted that EPA's legal interpretation of the scope of §4(f) directly contravenes earlier Agency interpretations of the provision. For example, in 1980, EPA's office of General Counsel prepared a "Primer" on §4(f) which states: "Section 4(f) states that EPA must designate a chemical as a priority candidate when information indicates that there 'may be a reasonable basis' to find that a high degree of risk exists from cancer, birth defects, or gene mutations. In contrast, the regulatory authorities provided by TSCA under §§5, 6, and 7 generally require EPA or a federal court to find that there 'is a reasonable basis to conclude' that an unreasonable risk to health or the environment is presented. It follows from the difference in language that a 4(f) designation requires less certainty as to the existence of a particular level of risk than the major regulatory provisions of TSCA require with respect to a finding of 'unreasonable risk.' This distinction is consistent with the different purposes served by these provisions. Section 4(f) designates candidates for expedited regulatory decisionmaking, and itself imposes no regulatory controls. Instead, it triggers a period of intensive study on whether the Agency should initiate action to control the substance; initiation is only the first step in a process which may eventually lead to promulgation of a regulation." Primer on TSCA §4(f),OTS,October 30, 1980.

> The calculated risk estimates suggest that a *high level of risk may be associated with a number of situations involving exposures to populations*. For most of the identified subpopulations the estimated risks are equal to or greater than $10^{-5}$; however, in some instances the risks are in the range of $10^{-1}$..., $10^{-2}$..., and $10^{-3}$.... [Executive Summary, p.IX (emphasis added)].

By contrast, the Technical Document on Formaldehyde of November 19, 1981 by EPA's OTS concluded:

> For most of the identified subpopulations, the estimated risks are equal to or greater than $10^{-5}$....

> Generally, the available information supports the view that formaldehyde has carcinogenic potential. That this potential poses a significant risk to humans is not supported by the evidence. [Executive Summary, Page IX (emphasis added)].

Concerning the carcinogenicity of formaldehyde, the TD includes four new pages of interpretation of the CIIT results (pp. 86-90) which strongly suggest that a threshold exists for the carcinogenicity of formaldehyde. In addition, the TD does not update the PRL-I concerning the NYU study demonstrating the carcinogenicity of formaldehyde although nine months had passed between the two reports. The TD also inserts sentences into the PRL-I discussion of previous (negative) bioassays of formaldehyde that lend them greater importance than in the PRL-I and that qualify the relevance of the CIIT study to humans.

The Todhunter Memorandum of February 10, 1982, concluded:[1]

> There is suggestive evidence that there may be human exposure situations -- based on the integrated animal data base -- which may not present carcinogenic risk which is of significance.... I must concur with OTS' staff recommendations in this matter -- that formaldehyde ought not to be considered subject to §4(f) at this time. (p. 12)

Although the memo does not specifically refer to the TD, it is apparently based upon the TD and not the PRL-I. Parts of the memo concerning policy and interpretation of data are drawn verbatim from the TD.

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[1] Todhunter Memorandum at 5, 12.

In his February 10 formaldehyde memo the Assistant Administrator for Pesticides and Toxic Substances also suggested that risks in the range of $10^{-4}$ (one in 10,000) to $10^{-6}$ (one in a million) are not of a magnitude usually considered to warrant regulatory action. By comparison, the Consumer Product Safety Commission banned urea formaldehyde foam insulation based on an estimated risk of $10^{-5}$ (one in 100,000). That EPA would disparage as insufficient merely to justify a closer look at formaldehyde,risks others consider sufficient to warrant a ban is troubling indeed.

Thus, EPA's initial conclusion that exposure to formaldehyde poses a significant risk to human health, sufficient to trigger §4(f) of TSCA, has been transformed into the contrary conclusion. There are no new data to support this reversal: only a reinterpretation advocated by and quite favorable to the interests of the formaldehyde industry. Those new assumptions depart radically from accepted principles of cancer risk assessment, lack a sound scientific basis, and leave the public subject to cancer risks that TSCA and other regulatory statutes were intended to protect against.

In order to "get government off the back" of the formaldehyde industry, EPA has engaged in a series of actions that we believe were procedurally improper and violative of the Agency's statutory duty under §4(f) of TSCA. Perhaps even more disturbing is the willingness of Dr. Todhunter and others at the highest levels of EPA to engage in Orwellian revisionist science to justify the decision not to act on formaldehyde. Such actions bode ill for the future protection of public health. They also constitute such disregard for the public interest as to raise serious questions about the fitness of the current leadership at EPA for the offices they hold.

Mr. **Gore**. Thank you very much.

Dr. Perera, in his answer to questions today Dr. Todhunter stated that CIIT considered the 1.9-percent response in rats exposed to 5.6 ppm as "not statistically significant," but Dr. Todhunter considered the carcinogenesis "biologically significant." Though the Todhunter memorandum on page 6 only mentions the lack of statistical significant and not biological significance, could you explain the difference between these statements and the significance of that difference, or is that impossible?

Dr. **Perera**. Well, I think I might have to look again at the Todhunter memo, the page to which you are referring.

Mr. **Gore**. Let me do this: We have a close vote on the floor. We will recess for about 7 minutes and then come back and you can look at in the meantime, and then we will start questions.

Dr. **Perera**. Sure. Fine.

[Recess taken.]

Mr. **Gore**. The subcommittee will come back to order.

Dr. Perera, my first question was about the distinction between statistical significance and biological significance. Do you want to respond?

Dr. **Perera**. Yes. I have found the statement on page 6 of the memo and it is in the section entitled "Interpretation Of Animal Studies With Respect To Human Risk." It does read that the 1.9 percent in rats at 5.6 ppm was not statistically significant. I am glad that Dr. Todhunter added during his testimony earlier the fact that he does consider them to be biologically significant because the statement as it reads in the memo could be misleading.

If in fact you look at the incidence of this very rare nasal tumor in control animals, in thousands of control animals used over a period of many years in different laboratories, you do appreciate the biological significance, the rarity of this tumor, and conclude that if you do use these historical controls you do have statistical significance at this dose level.

Mr. **Gore**. Very good.

Mr. Dailey, you were present at the so-called science court meetings conducted by Dr. Hernandez last summer, were you not?

Mr. **Dailey**. Yes, I was.

Mr. **Gore**. Did you feel as though all the views and expertise available were represented at these science court meetings?

Mr. **Dailey**. The agencies' expertise?

Mr. **Gore**. Well, the points of view that were pertinent to the issues under discussion, for example, the views of other agencies.

Mr. **Dailey**. There were no other agencies represented there that I can remember.

Mr. **Gore**. I see. What about public interest groups?

Mr. **Dailey**. There were no public interest groups.

Mr. **Gore**. It was just EPA and industry?

Mr. **Dailey**. It was EPA, the Formaldehyde Institute, the National Academy of Science had two members in attendance at one meeting——

Mr. **Gore**. Were they experts in formaldehyde, the NAS folks?

Mr. **Dailey**. I would say they were people who were fairly familiar with formaldehyde, yes. Also, members of the CIIT were present at different meetings.

Mr. GORE. Did you ever feel as though certain views were more closely scrutinized than others by the senior EPA personnel present?

Mr. DAILEY. Not particularly.

Mr. GORE. Now there was an incident during the science board meetings when Jane Keller—she was the epidemiologist at EPA, is that right?

Mr. DAILEY. Yes; that is correct.

Mr. GORE. Subsequently departed?

Mr. DAILEY. That is right.

Mr. GORE. There was an incident during the science board meetings when she discussed the epidemiological studies. Do you remember that incident?

Mr. DAILEY. Yes, I think I do.

Mr. GORE. Could you describe what happened?

Mr. DAILEY. Well, there was a discussion between the epidemiologist from the Formaldehyde Institute and Ms. Keller over a point on the relevance of each of the three studies that were under discussion, and Dr. Todhunter interjected and asked Ms. Keller a question. Before she could reply he asked her another question, and as she started to reply to that he asked her another question. She never got a chance to answer any of the questions that he asked before he cut her off in a very aggressive manner.

Mr. GORE. I see. Now she disagreed with the epidemiologist from the Formaldehyde Institute.

Mr. DAILEY. True, yes.

Mr. GORE. Dr. Todhunter sort of aggressively cut her off during questioning of her. Did he do the same thing with the epidemiologist from the Formaldehyde Institute?

Mr. DAILEY. No.

Mr. GORE. I see. That was an unusual procedure.

You mentioned the comments that began to come down from Dr. Todhunter's office in writing and mentioned that they caused you some concern. Now to clear up this matter in my own mind the PRL-1—PRL stands for what, again?

Mr. DAILEY. Priority review level 1.

Mr. GORE. Priority review level 1, and it is always called a PRL-1.

Mr. DAILEY. Right.

Mr. GORE. He actually made changes to the text of the PRL-1, is that correct?

Mr. DAILEY. That is what I was told. I was given a copy of the PRL with penciled changes, and I was told——

Mr. GORE. In what you were told was his handwriting.

Mr. DAILEY. It was his handwriting, they were his comments to be inserted verbatim.

Mr. GORE. Now was there another iteration of the PRL-1 or did it then become labeled the "Technical Documents"?

Mr. DAILEY. Well, I chose not to make those comments. I asked not to participate on the formaldehyde project at that point.

Mr. GORE. Because you felt it was unscientific, the changes that you were asked to make?

Mr. DAILEY. Well, as I explained, I called Dr. Hech, and this was on the endogenous formaldehyde point in particular, and felt that what I was being asked to do was not scientifically correct. Therefore, I did not want to participate.

Mr. **Gore**. Yes. You knew better.

Mr. **Dailey**. Right. I was told, "Don't worry, put these in."

Mr. **Gore**. Do it anyway.

Mr. **Dailey**. Do it anyway.

Mr. **Gore**. Who told you to do it anyway?

Mr. **Dailey**. This was my branch chief, my direct boss.

Mr. **Gore**. What is his name?

Mr. **Dailey**. Her name is Dr. Carol Mapes.

Mr. **Gore**. Dr. Carol Napes?

Mr. **Dailey**. Mapes.

Mr. **Gore**. Now it was told to you that these orders came from Dr. Todhunter?

Mr. **Dailey**. Yes.

Mr. **Gore**. I see. Now you refused to do that. What happened then?

Mr. **Dailey**. I was taken off the project.

Mr. **Gore**. I see. Did you ever see the PRL-1 again?

Mr. **Dailey**. No.

Mr. **Gore**. Therefore, it is possible that the changes were made to the PRL-1 and the heading was changed so that it became "Technical Documents."

Mr. **Dailey**. That is correct.

Mr. **Gore**. I believe that that is what——

Mr. **Dailey**. I think that is what happened. I know that there were several revisions subsequent to the penciled-in revisions that Dr. Todhunter wanted, before I ever saw the "Technical Document" again. I was completely out of the formaldehyde program for 3 months.

Mr. **Gore**. Well, if you were so concerned about these changes that you felt to be at odds with a valid scientific interpretation of the evidence, did others on the staff also express concern or puzzlement at some of Dr. Todhunter's comments?

Mr. **Dailey**. Yes.

Mr. **Gore**. All right.

Ms. Warren, you recently sent a letter to EPA about the then-PCB conference. Could you explain the purpose of this letter and the response you received?

Ms. **Warren**. Yes, I will. I just would like to briefly give you a little background.

The 1976 TSCA has a provision in it, section 6(e), in which Congress said to EPA, "Ban PCB's. Put out rules to govern the disposal of them, and then eliminate all but totally enclosed uses and phase out the manufacture and distribution in commerce of all PCB's except in certain cases where there is not an unreasonable risk from allowing those to continue."

EPA, under the last administration, put out a ban rule that exempted 99 percent of the PCB's in use from the coverage of the ban. The District of Columbia Circuit Court of Appeals threw out the ban regs, saying that a rule that reaches less than 1 percent of the PCB's in use is not consistent with Congress' direction to phase out PCB's.

EPA is now in the process of rewriting those rules. According to a court-ordered schedule, the PCB ban regulations have to be finished by the end of this year. About a month and a half ago EPA decided to empanel a symposium to look at recent advances in the health effects and environmental effects evidence on PCB's, and the letter that I wrote to Mrs. Gorsuch was a reflection of my concern that the people who were asked to present papers at that panel represented primarily the industries who would be adversely affected by the rewrite of the PCB ban rule. They did not, the panelists did not include very many PCB experts—in fact, there was only one person initially who was asked to appear, who had any direct experience with health effects research on PCB's. When the symposium actually took place it turned out that there were three people with direct experience on PCB's, but the issue of greatest concern to me was that the two industries that would be affected by the PCB ban regulations rewrite, which are the electric utilities and chemical manufacturers, hired consultants to review the very extensive literature on the health effects of PCB's and the consultants' literature reviewers concluded that PCB's are not hazardous.

Three of these industry consultants were presented at the EPA symposium as experts on the health effects of PCB's although none—there were two consultants for CMA and one consultant for the Edison Electric Institute—had any independent expertise on PCB's as researchers on the health effects of PCB's. Their expertise on the question, to the extent they had any, came from their having been hired by industry to review the literature on PCB's. Yet, they were presented as experts. People from Dow and Monsanto were presented as experts on the health and environmental effects of PCB's.

A woman named Renata Kimbrough from the Centers for Disease Control was asked to be a discussion leader. She had some direct experience with PCB health effects. She almost did not go to it because she was so concerned about the bias in the panel. That was why I wrote the letter to Mrs. Gorsuch saying, "In 1975 EPA had a 4-day conference in Chicago on PCB's at which everyone in the United States and elsewhere who was working on PCB research was invited to participate and present papers."

This symposium was thrown together in a very short period of time, and it was primarily industry people coming on to promote their recent conclusion that PCB's are not a hazard. I was concerned because I felt that it was an effort to pad the record of the PCB rulemaking. I think you are going to be hearing more about that.

I consider this effort on formaldehyde a reflection of the same attitude, which is to redefine the problems out of existence. If formaldehyde is not a risk, we do not have to worry about it. If PCB's are not hazardous, we do not have to worry about them. As I said before, I think that is not in the public interest and it does not have a firm scientific foundation either.

Mr. GORE. What kind of response did you get?

Ms. WARREN. I got a telephone call from Dr. Todhunter in which he read me a letter that he had written to me which said in fact there were only four industry affiliated people on the panel, the two from Dow and the two from Monsanto. I reiterated back again that there were three industry consultants who were also there, but he did not respond to that. He told me that this was a symposium, that he did not know how the people who were picked to appear had been chosen, it was not his symposium, it did not have anything to do with the rulemaking, it probably would not even be published for over a year.

However, our representative—someone representing me, as a matter of fact—attended a meeting in Don Clay's office with a representative of CMA to discuss PCB's at which the general counsel of CMA said, "Dr. Todhunter promised that this symposium would take place while the rulemaking record was open." Therefore, the implication is that it is an effort to pad the record and I am quite certain that the proceedings will appear in the rulemaking record.

Mr. GORE. Mr. Clement?

Mr. CLEMENT. Thank you, Mr. Chairman.

I would ask one thing, Mr. Chairman, at this point. I believe Ms. Warren asked earlier for permission to insert a legal opinion as to the effects of section 4(f) in the record. Is that not correct?

Ms. WARREN. Yes. It is the general counsel's opinion. I think it was written in October 1980. It is called Primer on Section 4(f).

Mr. CLEMENT. I would like the chairman's permission to include immediately after that a similar opinion from the general counsel at EPA.

Mr. GORE. Without objection, both documents will be put into the record. (See appendix 5 and appendix 6.) While we are on this, let me also put into the record, without objection, letters from Dr. Upton (see appendix 7); the records of the Hernandez science court meetings, the agenda and the attendees (see appendix 8); also a review of the Du Pont study by NIOSH and others which we are going to have done (see appendix 9); and also the comments by Dr. Todhunter to the PRL-1 and the "Technical Documents," the revisions that he made (see appendix 3). In addition is the report from Mt. Sinai on the carcinogenicity of formaldehyde (contained in appendix 4); the EPA staff critique of Formaldehyde Institute data (see appendix 10); and of course the Todhunter memo that has formed the basis of a lot of the hearing record (see appendix 1). Without objection, they will be put in at appropriate points in the record.

Mr. CLEMENT. Mr. Chairman, I must say I knew I was opening the door but I did not know it was going to fall off the tracks.

Mr. GORE. A lot of those we have been referring to earlier and we should have put them in earlier.

Mr. CLEMENT. Of course, Mr. Chairman.

I would like to ask one or two questions. Dr. Perera, your training apparently is that you are a doctor of public health.

Dr. PERERA. That is right.

Mr. CLEMENT. Do you have specific training in the field of molecular or cellular biology?

Dr. PERERA. No, I do not. My degree is in environmental health sciences from Columbia University.

Mr. CLEMENT. All right. In general, I think it is fair to say that you do not agree with Dr. Todhunter's concurrence with the decision memorandum. Is that correct?

Dr. PERERA. With the decision memorandum? Which one?

Mr. **CLEMENT**. Well, in essence you do not agree with the——

Dr. **PERERA**. I do not agree with Dr. Todhunter's assessment of the data.

Mr. **CLEMENT**. All right. Do you also disagree, that there is no such thing as a threshold level for cancer?

Dr. **PERERA**. I am glad you gave me this opportunity. I think I can say a little more than I did the first time around.

On this question, I have consulted with experts in the field of carcinogenesis, including researchers in the area of carcinogenesis promotion, and while I think there is some debate about the ease with which one can demonstrate an experimental threshold for a carcinogen, especially a promoter, there seems to be very general agreement that it is extremely difficult if not virtually impossible, using currently available methods, to identify a "population" threshold, that is a safe level for the human population. The reason for this is that, unlike animals used in bioassays, humans are genetically diverse and humans are also exposed to a great many carcinogenic substances, both initiators and promoters. Therefore, I do feel that there is a consensus on this point of the population threshold.

Mr. **CLEMENT**. Does that mean that you would disagree that there is a threshold or that it is very difficult to identify what that might be?

Dr. **PERERA**. Well, my remarks were general, relating to carcinogens in general. Specifically for formaldehyde, I believe that there is no evidence demonstrating a threshold for the carcinogenic effect.

Mr. **CLEMENT**. Are you familiar with the textbook, "Fundamentals of Oncology"?

Dr. **PERERA**. The one that was referred to by Dr. Todhunter?

Mr. **CLEMENT**. Yes.

Dr. **PERERA**. No, I am not.

Mr. **CLEMENT**. Are you familiar with the name, Dr. Henry Pitot?

Dr. **PERERA**. Yes, I am.

Mr. **CLEMENT**. Well, I am informed that he is the author of "Fundamental of Oncology," which is a standard text.

Dr. **PERERA**. Yes. I recall Dr. Todhunter's alluding to that.

Mr. **CLEMENT**. Let me quote you from a statement there:

> However, the production of neoplasia in animals at statistically higher levels than in controls has been considered indicative of carcinogenicity of the agent under study. Modern concepts of natural history of neoplastic development require that this simplistic evaluation of data be reconsidered.

Do you agree or disagree with that?

Dr. **PERERA**. Well, I think there he probably is speaking about experimental thresholds. I do not believe that Dr. Pitot would be extrapolating from those and from the possibility of establishing those in a laboratory system to a human population.

I did not read it but I had in my written testimony quoted a statement by Drs. Upton and Weinstein, who wrote a letter to EPA, CPSC, and OSHA which I refer to in my testimony, and I will quote if I may from their letter. They stated: "There is no recognized method as yet for determining the existence of a threshold for a carcinogen in the human population." At the end of the letter they note that they had consulted with a great many of their colleagues in the field of carcinogenesis research and policy.

Mr. **Gore**. If the gentleman will yield, Richard Pitot was one of the authors of the OTA report on the assessment of technologies for determining cancer risk from the environment, and that study concluded in part, and I quote:

> However, it is generally accepted that a population threshold which would define a risk-free dose for a group of people composed of diverse individuals, if it exists, cannot now be demonstrated. Federal agencies do not accept the idea of thresholds in making decisions about carcinogenic risks.

Thanks for yielding.

Mr. **Clement**. It is always a pleasure to yield to my chairman.

Ms. Warren, I am not even going to ask you a question. I have never met you before but I must say that I have heard your name any number of times in the environmental field, and you come with impeccable credentials. I would really like to say it is a pleasure to have finally met you.

Ms. **Warren**. I am disappointed that I am not getting a question.

Mr. **Clement**. I have learned not to open the door too frequently. [Laughter.]

There is one minor problem I would point out to my chairman, and that is that he has very correctly quoted Richard Pitot. However, I was referring to Dr. Henry Pitot, P-i-t-o-t, which is spelled differently.

Mr. **Gore**. Well, we have not seen what you are quoting from or what Dr. Todhunter was quoting from, so I apologize for the error.

Mr. **Clement**. Mr. Dailey, I do have a couple of questions about your data and your statement. I understand that you are a former employee of the Environmental Protection Agency.

Mr. **Dailey**. That is correct.

Mr. **Clement**. You began your statement saying that you are not appearing as an expert on chemical carcinogens, analytical monitoring methods, epidemiology, or any other discipline. Is that correct?

Mr. **Dailey**. That is correct.

Mr. **Clement**. I notice that we have been overcome with doctors today and you are a mister. Would you let me have some idea of what your educational background is?

Mr. **Dailey**. Yes. I have a degree in biology and chemistry and graduate work in environmental science.

Mr. **Clement**. You have a degree in biology and chemistry?

Mr. **Dailey**. Right.

Mr. **Clement**. You have a dual major?

Mr. **Dailey**. Yes.

Mr. **Clement**. Where is that degree from?

Mr. **Dailey**. From Tusculum College in Tennessee.

Mr. **Gore**. Another Tennessean on the panel. [Laughter.]

Thanks for bringing that out.

Mr. **Clement**. I opened the door one more time, Mr. Chairman.

All right. You say you have graduate studies in environmental science?

Mr. **Dailey**. Right.

Mr. **Clement**. Do you have a graduate degree?

Mr. **Dailey**. No, I do not.

Mr. **Clement**. You do not? Where were those graduate studies?

Mr. **Dailey**. At American University.

Mr. **Clement**. At American? All right. Therefore, you have a bachelor of arts degree, then.

Mr. **Dailey**. A bachelor of science degree.

Mr. **Clement**. A B.S. All right. You state that your job was a generalist. Let me ask you: With a bachelor's degree, you say that you were—part of your job function was to analyze, interpret, and synthesize scientific information?

Mr. **Dailey**. That is correct..

Mr. **Clement**. Do you feel educationally qualified or qualified by your previous work experience to analyze, interpret, and synthesize the work of people working at the doctorate level?

Mr. **Dailey**. I feel that I have the capability to understand what those people are talking about, yes, and as I said, to synthesize very diverse disciplines into reports that I had to make to management.

Mr. **Clement**. Do you have graduate training in cellular biology?

Mr. **Dailey**. No.

Mr. **Clement**. Do you have graduate training in molecular biology?

Mr. **Dailey**. No, I do not.

Mr. **Clement**. Have you taken courses in oncology?

Mr. **Dailey**. Yes, I have.

Mr. **Clement**. At what level?

Mr. **Dailey**. I took a graduate course in toxicology. I also took a course at MIT in toxicology.

Mr. **Clement**. You also have a statement here that rather bothers me, in the fact that I think some of the facts here may have perhaps been thrown around. You say you did not volunteer information on this issue to members of the investigation team of the subcommittee, and are only appearing reluctantly at the direction of the chairman. Have you been approached by anyone else for your views on this issue?

Mr. **Dailey**. Yes, I have.

Mr. **Clement**. Who would that be?

Mr. **Dailey**. I have been approached by a number of reporters, both broadcast and print.

Mr. **Clement**. Have you shared your views with any of them?

Mr. **Dailey**. Occasionally, yes.

Mr. **Clement**. Have you been quoted by any of them by name?

Mr. **Dailey**. No.

Mr. **Clement**. Your name has not appeared in the pesticide and toxic chemical news?

Mr. **Dailey**. Not to my knowledge.

Mr. **Clement**. However, in fact you have cooperated with other people who were looking into this area?

Mr. **Dailey**. Yes, I have.

Mr. **Clement**. All right. On page 6 of your testimony you have two statements I would like a little further information on. First, in the top paragraph you say several scientists from CPSC and OSHA, both of whom have had extensive knowledge in the carcinogenic and epidemiological aspects of formaldehyde, asked for and were denied permission to attend the mission. Would you care to identify who those people were?

Mr. DAILEY. Yes. It was Dr. Andrew Ulsamer from CPSC and Dr. Han Kong from OSHA.

Mr. CLEMENT. Do you know who purportedly denied them access?

Mr. DAILEY. No, I do not.

Mr. CLEMENT. In the next to last paragraph, you say you questioned some of the changes that were to be made but were ordered to incorporate Dr. Todhunter's comments verbatim. I assume that was where you said Dr. Mapes directed you to include comments?

Mr. DAILEY. That is correct.

Mr. CLEMENT. That is correct.

All right. On the last page, you say that the document was returned several days later with handwritten comments from Dr. Todhunter ordering more changes. Can you identify what those changes were?

Mr. DAILEY. The changes he asked for at that point, they were rather vague. He said that he wanted to say something about virtually safe doses, and also that we include—because in the version that I rewrote, we totally left out any attempt at quantitative risk assessment. There was no quantitative risk at all. In his handwritten comment on that version, he said that he wanted to use maximum likelihood estimates using midpoint exposures of populations of known sizes.

Mr. CLEMENT. Therefore, in fact at that point he was saying that the risk number should in fact stay in the document?

Mr. DAILEY. Yes.

Mr. CLEMENT. I have no further questions of this panel, Mr. Chairman.

Mr. GORE. All right. Thank you.

We are going to put all of those changes in the record under a previous permission.

I would like to thank all of you. Mr. Dailey, I should like to congratulate you on your courage and candor. After 5½ years in the Congress on investigations subcommittees, I have learned to really appreciate the rare individuals who, when asked to do something that they believe to be contrary to their convictions, are willing to stand up and say, "This is not right." I really do admire your courage in that regard and I wish we had a lot more people like you. Thank you very much.

Dr. Perera, Ms. Warren, I continue to appreciate the fine work that you all do on a continuing basis and appreciate your help here today. Thank you very much.

Our final panel is made up of Dr. James Gibson with CIIT, Dr. Robert L. Sielken, Jr., with Texas A&M, and Dr. Sorell Schwartz from Georgetown University.

Gentlemen, I am sorry that we have kept you waiting throughout this long proceeding. I appreciate your patience, as does the subcommittee. We would like to swear you in, if you would stand and raise your right hands, please.

Do you swear the testimony you are about to give will be the truth, the whole truth, and nothing but the truth, so help you God?

Dr. GIBSON. I do.

Dr. SIELKEN. I do.

**Dr. Schwartz.** I do.

**Mr. Gore.** Thank you very much.

Now do you all have prepared statements? Do you have written statements?

**Dr. Sielken.** No, I do not have a written statement. I do have some transparencies that I hope to show.

**Dr. Schwartz.** My statement, I have a handwritten statement which I prepared during the hearings today but nothing that has been prepared for distribution.

**Mr. Gore.** Dr. Gibson, do you have a prepared statement?

**Dr. Gibson.** I have a statement that I can have read into the record.

**Mr. Gore.** I see. Well, it is an unusual procedure. We are going to go forward nonetheless out of courtesy to the minority. It is customary for witnesses to provide statements in advance to the subcommittee, a short time in advance, so we have an opportunity to review the statements. It is most unusual to call witnesses and have them sit through the hearing and then give them an opportunity to come in at the end and respond. It really should not be done this way but we are going to do it as a matter of courtesy.

However, let me just make it clear for the record that we are going outside the normal bounds of procedure. Each one of you has been requested to testify by the minority. Is that correct?

**Dr. Gibson.** Yes.

**Dr. Sielken.** Yes.

**Dr. Schwartz.** Yes.

**Mr. Gore.** OK.

**Mr. Clement.** Mr. Chairman?

**Mr. Gore.** Yes?

**Mr. Clement.** Would the chairman yield for a moment?

**Mr. Gore.** Sure.

**Mr. Clement.** I would like to apologize to the chairman for this unusual procedure. The panel before us is appearing at the request of the minority. They were only asked in the last 48 hours, and the reasons are that Dr. Gibson is with CIIT and was intimately familiar and responsible for the conduct of the studies that have been the subject of much discussion here today. He has been asked to come and explain what the Institute was looking for, what they believe they found, and what the significance of those findings are.

Dr. Sielken is an eminent statistician with Texas A&M University who has seen the data in the past and has worked with it. We have asked him to come and explain what he thinks the results mean statistically and how he arrived at those terms.

Dr. Schwartz I only talked to for the first time night before last at about 11 p.m. He has a very good reputation in the scientific community. He teaches scientific risk assessment through Georgetown University and he has been asked to come in essentially as an honest broker and to discuss risk assessment as it should take place in the governmental forum. I have not had a chance with Dr. Schwartz specifically to have any opportunity to guide him one way or the other. He is going to be strictly reacting.

**Mr. Gore.** As opposed to the other two?

**Mr. Clement.** I have seen Dr. Gibson's printed materials, his literature, in the past; I have seen Dr. Sielken's statistical analysis.

Mr. **Gore**. I see. All right. Now we do not even have biographies. It is most unusual. Let me just ask you, do you all have biographies with you, incidentally?

Dr. **Gibson**. Yes.

Dr. **Schwartz**. Yes.

Mr. **Gore**. The two of you that do, could you give them to the staff here?

Have you all worked as consultants to the Formaldehyde Institute, by any chance?

Dr. **Sielken**. I did act as a consultant to FDA, EPA, and also the Formaldehyde Institute.

Mr. **Gore**. Dr. Schwartz?

Dr. **Schwartz**. I did not act as a consultant to the Formaldehyde Institute but I did act as a consultant to one of the litigants in the Massachusetts case. The Formaldehyde Institute was one of the litigants but I was not a consultant to them.

Mr. **Gore**. You were a consultant to one of the manufacturers of formaldehyde?

Dr. **Schwartz**. That is correct, the manufacturers of the tripolymer foam.

Mr. **Gore**. Dr. Gibson?

Dr. **Gibson**. No, I have not been a consultant to the Formaldehyde Institute.

Mr. **Gore**. Have you been—oh, you are with the industry group. You are with the CIIT. Correct?

Dr. **Gibson**. That is correct.

Mr. **Gore**. You are the vice president of the CIIT.

OK., are any of the three of you being paid for your testimony here today by the Formaldehyde Institute?

Dr. **Gibson**. I am not being paid.

Dr. **Sielken**. Nor am I.

Mr. **Gore**. Dr. Sielken, if you could provide a biography for the record, we would appreciate it.

Mr. **Clement**. Mr. Chairman, I would also like to point out that Dr. Schwartz not only has appeared in court for manufacturers in this process, he has also appeared as an expert witness in court for the Government, and for consumer groups in other actions. Is that not correct, Dr. Schwartz?

Dr. **Schwartz**. That is correct, but not on formaldehyde.

Mr. **Gore**. You never appeared as the witness for consumer groups on formaldehyde?

Dr. **Schwartz**. Not on formaldehyde, no.

Mr. **Gore**. You have only appeared for the industry on formaldehyde?

Dr. **Schwartz**. Yes. I have only had one appearance.

Mr. **Gore**. All right. We will begin with you, Dr. Gibson.

## STATEMENT OF DR. JAMES E. GIBSON, VICE PRESIDENT AND DIRECTOR OF RESEARCH FOR THE CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

Dr. **Gibson**. Thank you very much, Mr. Chairman. I am James E. Gibson, vice president and director of research for CIIT, the Chemical Industry Institute of Toxicology, a position I have held for 5½ years since the Institute was founded. The CIIT is a nonprofit, independent public institution that is engaged in testing, research, and training in toxicology. It is supported financially by the industry.

Much has been said today about the CIIT studies with formaldehyde. I would like to speak to those studies and those studies only today. I will paraphrase a presentation I made recently on these studies at the International Particleboard Symposium held at Washington State University in March of this year. A copy of that presentation has been made available to the subcommittee.

Mr. Gore. This is one of the industries that makes the largest use of formaldehyde, is it not?

Dr. Gibson. Yes, the particleboard industry is a large user of formaldehyde.

Mr. Gore. Go ahead.

Dr. Gibson. However, this was a university-based symposium on the subject of particleboard technology.

A 30-month chronic inhalation toxicity and carcinogenicity study of formaldehyde vapor in male and female Fisher 344 rats and B6C3F1 mice was sponsored by the Chemical Industry Institute of Toxicology. The study, conducted by the Battelle Memorial Institute, Columbus Laboratory, utilized 960 rats and 960 mice. One hundred and twenty animals of each species and sex were exposed to either 0, 2, 6, or 15 ppm of formaldehyde vapor, 6 hours per day, 5 days per week.

During 24 months of inhalation exposure, approximately one-half of the rats exposed to the highest exposure concentration developed squamous cell carcinomas of the nasal cavity or, to a much lesser extent, other tumors of the nasal cavity. The earliest tumors were discovered between the 11th and 12th months of exposure in rats exposed to 15 ppm of formaldehyde.

In comparison to rats, mice were substantially resistant to these effects, although they were exposed to formaldehyde simultaneously in the same chambers. In two mice exposed to 15 ppm only, squamous cell carcinomas were discovered after the 24th month of exposure was completed, during examination of tissues taken at the planned necropsy. Two rats with squamous cell carcinomas in the nasal cavities were also found following exposure to 6 ppm formaldehyde for 24 months.

Therefore, both the time of tumor development as well as the sensitivity to tumor formation for formaldehyde was species- and dose-dependent. Squamous cell carcinomas are not found to occur spontaneously in the nasal cavities of rats and mice.

The interpretation of the results I have just presented concerning the assessment of risk for formaldehyde exposure requires a detailed understanding of the mechanisms involved in the observed neoplastic response. Research at CIIT has provided some of the necessary knowledge for understanding the results of the long-term studies, and is based on a multi-stage mechanistic model.

The reactivity and water solubility of formaldehyde limits most exposure to the nasal cavities of obligatory nose-breathing species such as rats and mice. Both autoradiography and classical disposition studies in rats using carbon-14 labeled formaldehyde have demonstrated the localization of radioactivity in the nasal epithelium. Smaller amounts reached the trachea, lung, and plasma during inhalation of carbon-14 formaldehyde in rats. The amount of radioactivity was one to two orders of magnitude greater in the nasal mucosa than in plasma, lung, liver, kidney, testes, or brain.

Consistent with this finding, it is important to note that the toxic effects of formaldehyde observed in the CIIT long-term inhalation study were restricted to the upper respiratory tract, primarily the nasal cavity. It is unknown at present whether there are differences in sensitivity among the cell types in the nasal epithelium. The nasal epithelium is comprised of a number of cell types, including ciliated and nonciliated cells, and conceivably this is important in determining species sensitivity.

An additional feature of the respiratory tract that may influence formaldehyde toxicity is the respiratory tract mucous. The mucous is comprised of large, extended glycoprotein molecules having high carbohydrate content. The mucous may provide protection of respiratory epithelial cells at low concentrations of formaldehyde exposure, a protective mechanism lost at high formaldehyde concentration. Some of the effects of formaldehyde may influence mucous secretion, and in the CIIT study, rats from all formaldehyde groups has goblet cell hyperlasia of the respiratory epithelium after 24 months.

Among the biological effects of formaldehyde are the elicitation of physiological compensatory responses as well as metabolic interventions, all of which may prevent or diminish the prospect of any additional cellular interactions. The exhalation of carbon 14 0(2) in expired air of rats exposed to carbon-14 labeled formaldehyde by inhalation indicated extensive formaldehyde metabolism approximately 40 percent of inhaled formaldehyde was eliminated by this route.

The metabolism of formaldehyde to formate, catalyzed by formaldehyde dehydrogenase, is an oxidation reaction that may become limiting at high formaldehyde concentrations due to a dependence on the supply of cofactors such as NAD or glutathione. Glutathione participates by forming a formaldehyde hemithioacetal adduct which is the true formaldehyde dehydrogenase substrate. Repeated exposure of rats to formaldehyde by inhalation had no effect, however, on the specific activities of formaldehyde dehydrogenase or aldehyde dehydrogenase, or on the concentration of nonprotein sulfhydryls—primarily glutathione, in the nasal mucosa.

Moreover, the total formaldehyde concentration in nasal mucosa was not increased by repeated exposure to 6 or 15 ppm of formaldehyde by inhalation when analyzed by gas chromatography mass spectrometry. Thus, the major mechanisms for formaldehyde metabolism appear to remain intact even at high exposure concentrations. However, in acute toxicity studies with formaldehyde in rats, cell degeneration, necrosis, and inflammation were prominent responses noted in the nasal cavities following 1 to 9 days of exposure to 15 ppm, 6 hours per day. This was followed by ulceration, necrosis, and an influx of inflammatory exudate at later times in the nasal cavities.

Adaptive responses were also evident as a sequelae to the acute tissue damage produced by formaldehyde inhalation in rats. These included alterations in cell types such as squamous metaplasia and epithelial hyperplasia. There is no doubt, however, that acute exposures to 15 ppm of formaldehyde in rats caused cell death and ulceration in the nasal cavities.

Other effects of formaldehyde included interactions with cellular macromolecules. NCA alkaline elution studies have shown macromolecular cross-linking. The mechanism involves a formation of stable methylene bridges between macromolecules. The consequences of these interactions, however, are not known but may include damage to DNA and/or cell death.

One important feature in the toxicologic response of rats and mice to formaldehyde involves the measurement of the dose of formaldehyde reaching the nasal epithelium. Mice were more sensitive than rats to sensory irritation effects of formaldehyde, and equal concentrations of formaldehyde in air elicited a greater reflex slowing of respiratory rate in mice than in rats. Calculated on the basis of micrograms of formaldehyde reaching the nasal epithelium per mintute per unit of surface area, therefore, rats received approximately twice the dose of mice at 15 ppm. The difference in dose accounts for the observed difference in species sensitivity to formaldehyde.

These observations suggest that the expression of dose formaldehyde should be as an "effective dose" rather than as a concentration in air.

Formaldehyde mutagenicity has been reported for bacteria, fungi, and mammalian cells, but in other studies other mammalian cells have not responded, nor has formaldehyde been found to be a mutagen in the dominant lethal tests. Depending on the concentrations, on the conditions of the assay, both positive and negative findings have been obtained in Ames strains of Salmonella. In contrast to those mixed results, formaldehyde was a pure initiator of carcinogenesis in the 10T1/2 cell transformation assay. A dose-related increase in transformed foci was found to be induced by formaldehyde in the presence of a promoting agent. Formaldehyde, however, was not a complete carcinogen in these experiments since the presence of the promoter was required for transformation.

The in vitro genetic toxicity studies indicated the potential for DNA damage within cells of the nasal mucosa during formaldehyde exposure. Opportunities for repair of damaged DNA exist, however, and DNA repair may modulate genetic injury at sites of damage. The repair process was shown to be active for formaldehyde in a recent paper reported at the American Association for Cancer Research.

At low concentrations of formaldehyde, DNA repair may operate sufficiently to prevent chemical mutations. At higher concentrations of chemical exposure, repair may be saturated and unable to repair formaldehyde-induced DNA damage. Such mutational events may serve to initiate carcinogenesis, and in the presence of promotion, tumorigenesis may occur in the nasal epithelium. Conceivably, one promotional process could be the dose-related increase in cell proliferation in the nasal epithelium of rats which accompanied exposure to high concentrations for formaldehyde.

It should be stressed that the results of various genetic toxicity studies are mixed; some are positive and some are not. Research by CIIT indicates that the potential genetic toxicity of formaldehyde occurs only in dividing cells. The increase in cell proliferation brought about by acute tissue damage due to high concentrations of formaldehyde produced such a circumstance. In the nasal mucosa, the normal rate of cell division is very low and the rate in not increased by formaldehyde concentrations of 0.5 or 2 ppm in rats or by 0.5, 2, or 6 ppm in mice.

It seems reasonable from all this that many stages are involved in the process of formaldehyde-induced carcinogenesis. Some of these processes may operate to limit the effects of formaldehyde leading to carcinogenesis. Intuitively this seems reasonable, since formaldehyde is an endogenous biochemical which is constantly being produced and consumed in normal biochemical processes.

Risk analysis for formaldehyde-induced carcinogenicity must account for the various biological processes involved. Unfortunately, a complete understanding of the mechanism of formaldehyde's carcinogenicity in rats is not known, and no explicit method can be constructed to predict formaldehyde risk in man from the rat data. Virtually the same situation exists for all other animal carcinogens. Despite this, many approaches for low-dose extrapolation and risk assessment have been devised, and some even applied to the formaldehyde data, as we have already heard today.

The predicted concentrations of formaldehyde associated with the probability of tumor formation in rats, using some of these various models, have also been calculated by me. The probit, logit, Weibull, gamma multihit and multistage models essentially behave alike, while linear extrapolation seems to behave quite differently. The conclusions are the same whether the analyses are conducted on the absolute number of tumors observed in all the animals examined or on the adjusted data where the incidence of tumors is expressed per number of animals at risk.

An important perspective on the validity of the various models can be obtained by using the multistage model to predict tumor incidence in mice. Mice were exposed to formaldehyde simultaneously with rats in the CIIT study. If the rat data are used to predict nasal tumors in mice after 24 months of formaldehyde exposure to 15 ppm, 37 out of the 60 mice remaining at the 24th month should have had nasal tumors.

Actually, only two mice developed nasal tumors and these were microscopic. Furthermore, their incidence was not statistically significant. Thus, the rat data does not predict accurately the toxicity or carcinogenicity of formaldehyde in mice. This in turn calls into question the accuracy of the model for predicting carcinogenicity in man. Thus, risk assessment across species, as from rat to mouse or to humans, is in most cases an extremely inexact procedure.

2. Low-dose extrapolation by CIIT of the CIIT rat and mouse data for the purpose of human risk assessment must await additional knowledge on our part of the mechanism of formaldehyde's effects. Specific information on endogenous concentrations of formaldehyde in human tissues, cytological effects, occupational health effects, and mortality experience in humans must also be collected to fully understand formaldehyde's potential carcinogenesis in humans. The significance of the carcinogenic effects in rats, however, dictates that formaldehyde should be kept at the lowest possible concentration in the workplace, in homes, and in ambient air.

Thank you very much, Mr. Chairman, for the opportunity to make this statement.

[The prepared statement of Dr. Gibson follows:]

# MECHANISMS OF FORMALDEHYDE TOXICITY AND CARCINOGENICITY IN LABORATORY ANIMALS

James E. Gibson
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Running Head: Formaldehyde Toxicity

Presented at the International Particleboard Series, Symposium No. 16, Compton Union Building, Washington State University, Pullman, Washington, March 30, 1982.

## ABSTRACT

Formaldehyde toxicity was determined in Fischer-344 rats and B6C3F1 mice during long-term inhalation exposure. Rats and mice were exposed to formaldehyde concentrations of 0, 2, 6, or 15 ppm, 6 hrs/day, 5 days/week for twenty-four months. Following twenty-four months of formaldehyde exposure a significant incidence of squamous cell carcinomas of the nasal cavity was observed in rats exposed to 15 ppm. The inhalation of formaldehyde for twenty-four months was also associated with an exposure-related increase in the frequency, severity, and distribution of squamous metaplasia of the respiratory epithelium lining the anterior portion of the noses in rats from all exposure groups. In contrast to the rat, irritant-induced effects in mice were noted at only the highest exposure concentration. Additional studies of formaldehyde toxicity in rats and mice have shown that formaldehyde's effects are restricted to the nasal cavity, the primary site of contact during inhalation exposure. Formaldehyde disposition was largely restricted to the nasal cavity of both species and the dose to the nasal cavity was two times greater in rats than in mice. A respiratory reflex slowing of respiration which was pronounced in mice accounted for the dose differential. In rats, 15 ppm of formaldehyde caused acute cell injury and cell death as well as an increase in cell proliferation in the nasal mucosa at 6 and 15 ppm. Cell injury and cell proliferation was correlated with formaldehyde carcinogenesis. Formaldehyde, a normal endogenous biochemical that is continuously produced and consumed by normal cells, did not affect its own metabolism even at high concentrations. Studies of the potential for formaldehyde to induce genetic toxicity produced mixed results. Proper formaldehyde risk assessment requires a clear and complete understanding of the mechanism of formaldehyde's effects. One important feature of risk assessment, however, has emerged, namely the need to express dose as the amount of formaldehyde reaching the target tissue, not its concentration in air.

## INTRODUCTION

Formaldehyde is widely used for the production of materials important in modern society, including resins, textiles, particleboard, and plywood. Formaldehyde is also an important endogenous biochemical occurring in most life forms. Until recently very little was known about the potential chronic toxicity and carcinogenicity of formaldehyde.

Formaldehyde, in sufficiently high concentrations, is known to cause irritation effects of the skin, eyes, nose, and throat in exposed humans. However, physiological defense mechanisms usually prevent humans from subjecting themselves to these irritating concentrations of the chemical. Additionally, since formaldehyde occurs normally within cells, human exposure to slight amounts of formaldehyde might be assimilated without toxic effects. In normal cells formaldehyde in its "active" form ($N^5$, $N^{10}$-methylene-tetrahydrofolic acid) is necessary for the biosynthesis of purines, certain amino acids and other important biomolecules. However, the carcinogenicity of formaldehyde in rats due to inhalation of high concentrations of formaldehyde for long periods of time has raised additional concerns for human exposure.

A 30-month chronic inhalation toxicity and carcinogenicity study of formaldehyde vapor in male and female Fischer-344 rats and B6C3F1 mice was sponsored by the Chemical Industry Institute of Toxicology. The study, conducted by the Battelle Memorial Institute, Columbus Laboratory, utilized 960 rats and 960 mice. One hundred twenty animals of each species and sex were exposed to either 0, 2, 6, or 15 ppm of formaldehyde vapor 6 hours/day, 5 days/week. During 24 months of inhalation exposure approximately one-half of the rats exposed to the highest exposure concentration developed squamous cell carcinomas of the nasal cavity (Tables 1 and 2), or to a much lesser extent other tumors of the nasal cavity (1,2,3). The earliest tumors were discovered between the 11th and 12th month of exposure in rats exposed to 15 ppm of formaldehyde. In comparison to rats mice were substantially resistant to these effects although they were exposed to formaldehyde simultaneously in the same chambers. In two mice exposed to 15 ppm only squamous cell carcinomas were discovered after the 24th month of exposure was completed, during examination of tissues taken at the planned necropsy. Two rats with squamous cell carcinomas in the nasal cavities were also found following exposure to 6 ppm formaldehyde for 24 months. Therefore, both the time of tumor development as well as the sensitivity to tumor formation for formaldehyde was species- and dose-dependent. Normally squamous cell carcinomas are not found to occur spontaneously in the nasal cavities of rats and mice.

The interpretation of the results presented above concerning the assessment of risk for formaldehyde exposure requires a detailed understanding of the mechanisms involved in the observed neoplastic reponse. Research at CIIT has provided some of the necessary knowledge for understanding the results of the long-term studies and is based on a multi-stage mechanistic model (Figure 1).

## DISPOSITION OF FORMALDEHYDE

The reactivity and water solubility of formaldehyde limits most exposure to the nasal cavity of obligatory nose breathing species such as rats and mice. Both autoradiography (4) and classical disposition studies in rats (5,6) using $^{14}$C-formaldehyde have demonstrated the localization of radioactivity in the nasal epithelium. Smaller amounts reached the trachea, lung and plasma during inhalation of $^{14}C$-formaldehyde in rats. The amount of radioactivity was one to two orders of magnitude greater in the nasal mucosa than in plasma, lung, liver, kidney, testes, or brain. Consistent with this finding it is important to note that the toxic effects of formaldehyde observed in the CIIT long-term inhalation study were restricted to the nasal cavity. It is unknown at present whether there are differences in sensitivity among the cell types in the nasal epithelium. The nasal epithelium is comprised of a number of cell types including ciliated and non-ciliated cells (7) and conceivably this is important in determining species sensitivity.

An additional feature of the respiratory tract that may influence formaldehyde toxicity is the respiratory tract mucous. The mucous is comprised of large, extended glycoprotein molecules having high carbohydrate content. The mucous may provide protection of respiratory epithelial cells at low concentrations of formaldehyde exposure, a protective mechanism lost at high formaldehyde concentrations. Some of the effects of formaldehyde may influence mucous secretion; and in the CIIT study, rats from all formaldehyde groups had goblet cell hyperplasia of the respiratory epithelium after 24 months (1).

## CELLULAR INTERACTIONS

Among the biological effects of formaldehyde are the elicitation of physiological compensatory responses as well as metabolic interventions, all of which may prevent or diminish the prospect of any additional cellular interactions. The exhalation of $^{14}CO_2$ in expired air of rats exposed to $^{14}C$-formaldehyde by inhalation indicated extensive formaldehyde metabolism, and approximately 40% of inhaled formaldehyde was eliminated by this route.

The metabolism of formaldehyde to formate, catalyzed by formaldehyde dehydrogenase, is an oxidation reaction that may become limiting at high formaldehyde concentrations due to a dependence on a supply of cosubstrates such as NAD+ or glutathione (5). Glutathione participates by forming a formaldehyde hemithioacetal adduct which is the true formaldehyde dehydrogenase substrate. Repeated exposure of rats to formaldehyde by inhalation had no effect however on the specific activities of formaldehyde dehydrogenase or aldehyde dehydrogenase, or on the concentration of non-protein sulfhydryls (glutathione) in nasal mucosa (6). Moreover, the total formaldehyde concentration in nasal mucosa was not increased by repeated exposure to 6 or 15 ppm of formaldehyde by inhalation when analyzed by gas chromatography mass spectrometry (6,8). Thus the major mechanisms for formaldehyde metabolism appear to remain intact even at high exposure concentrations. However, in acute toxicity studies with formaldehyde in rats cell degeneration, necrosis and inflammation were prominent responses noted in the nasal cavities following 1 to 9 days (6 hours/day) of exposure to 15 ppm. This was followed by ulceration, necrosis and an influx of inflammatory exudate at later times in the nasal cavities (4).

Adaptive responses were also evident as a sequelae to the acute tissue damage produced by formaldehyde inhalation in rats. These included alterations in cell type such as squamous metaplasia and epithelial hyperplasia (4). There is no doubt, however, that acute exposures to 15 ppm of formaldehyde in rats caused cell death and ulceration in the nasal cavities.

Other effects of formaldehyde included interactions with cellular macromolecules. DNA alkaline elution studies have shown macromolecular cross-linking (4,9). The mechanism involves the formation of stable methylene bridges between macromolecules. The consequences of these interactions, however, are not known but may include cell death.

## RESPIRATORY COMPENSATION

One important difference in the toxicologic response of rats and mice to formaldehyde involves the measurement of the dose of formaldehyde reaching the nasal epithelium. Mice were more sensitive than rats to sensory irritation effects of formaldehyde and equal concentrations of formaldehyde in air elicited a greater reflex slowing of respiratory rate in mice than in rats. Calculated on the basis of μg formaldehyde reaching the nasal epithelium per minute per unit of surface area, therefore, rats received approximately twice the dose of mice at 15 ppm (10,11). This difference in dose accounts for the observed difference in species sensitivity to formaldehyde.

These observations suggest that the expression of dose metameter for formaldehyde should be as an "effective dose" rather than as a concentration in air.

## GENETIC TOXICITY

Formaldehyde mutagenicity has been reported for E. coli, fungi and L5178Y mouse lymphoma cells, but not in the CHO/HGPRT assay or in dominant lethal studies. Depending on the conditions of the assay both positive and negative findings were obtained in Ames strains of Salmonella (12). In contrast, formaldehyde was a pure initiator of carcinogenesis in the 10T½ cell transformation assay (13,14). A dose-related increase in transformed foci was found to be induced by formaldehyde in the presence of a promoting agent, 12-O-tetradecanoyl phorbol-13-acetate. Formaldehyde, however, was not a complete carcinogen in these experiments since the presence of the promoter was required for transformation.

The *in vitro* genetic toxicity studies indicated the potential for DNA damage within cells of the nasal mucosa during formaldehyde exposure. Opportunities for repair of damaged DNA exist, however, and DNA repair may modulate genetic injury at sites of damage. At low concentrations of formaldehyde, DNA repair may operate sufficiently to prevent chemical mutations. At higher concentrations of chemical exposure, repair may be saturated and unable to repair formaldehyde-induced DNA damage. Such mutational events may serve to initiate carcinogenesis, and in the presence of promotion, tumorigenesis may occur in the nasal epithelium. Conceivably one promotional process could be the dose-related increase in cell proliferation in the nasal epithelium of rats which accompanied exposure to high concentrations of formaldehyde (4).

It should be stressed that the results of various genetic toxicity studies are mixed; some are positive and some are not. Research by CIIT indicates that the potential genetic toxicity of formaldehyde occurs only in dividing cells. The increase in cell proliferation brought about by acute tissue damage dume to high concentrations of formaldehyde produce such a circumstance. In the nasal mucosa the normal rate of cell division is very low, and that the rate is not increased by formaldehyde concentrations of 0.5 or 2 ppm in rats or by 0.5, 2 or 6 ppm in mice.

## A MULTI-STAGE PROCESS

It seems reasonable that many stages are involved in the process of formaldehyde-induced carcinogenesis. Some of these processes may operate to limit the effects of formaldehyde leading to carcinogenesis. Intuitively this seems reasonable since formaldehyde is an endogenous biochemical which is constantly being produced and consumed in normal biochemical processes.

## RISK ASSESSMENT

Risk analysis of formaldehyde-induced carcinogenicity must account for the various biological processes involved. Unfortunately, a complete understanding of the mechanism of formaldehyde's carcinogenicity in rats is not known, and no explicit method can be constructed to predict formaldehyde risk in man from the rat data. Virtually the same situation exists for all other animal carcinogens. Despite this, many approaches for low-dose extrapolation and risk assessment have been devised (15), and some even applied to the formaldehyde data as discussed below.

Linear extrapolation is one method that considers that the probability of tumor formation is directly proportional to carcinogen dose. Every dose, no matter how small, would be expected to carry some probability of tumor formation (16). Linear extrapolation into the low-dose region for formaldehyde is not appealing because formaldehyde is present in normal cells as an essential metabolic intermediate.

Other statistical or stochastic models have been suggested to obviate the inherent problems of linear extrapolation. These include the probit, logit and Weibull distributions, as well as the gamma multi-hit and multistage models (17). These models also fail to account for formaldehyde's effects mechanistically at high and low concentrations and, therefore, at best could only approximate the expected response at low exposure concentrations.

The predicted concentrations of formaldehyde associated with the probability of tumor formation in rats using these models have been calculated (18). The probit, logit, Weibull, gamma multi-hit, and multistage models essentially behave alike, while linear extrapolation seems to grossly overprotect (Table 3). The conclusions are the same whether the analyses are conducted on the absolute number of tumors observed in all of the animals examined (Table 3) or on the adjusted data where the incidence of tumors is expressed per number of animals at risk (Table 4).

An important perspective on the validity of the various models can be obtained by using the multi-stage model to predict tumor incidence in mice. Mice were exposed to formaldehyde simultaneously with rats in the CIIT study. If the rat data are used to predict nasal tumors in mice after twenty-four months of formaldehyde exposure to 15 ppm, thirty-seven out of the sixty mice remaining at the twenty-fourth month should have had nasal tumors.

-Actually, only 2 mice developed nasal tumors and these were microscopic in size. Furthermore, their incidence was not statistically significant. Thus the rat data does not predict accurately the toxicity or carcinogenicity of formaldehyde in mice. This, in turn, calls into question the accuracy of the model for predicting carcinogenicity in man. Thus risk assessment across species, as from rat to mouse or to humans is in most cases, an extremely inexact procedure.

Low-dose extrapolation of the CIIT rat and mouse data for the purpose of human risk assessment must await additional knowledge of the mechanism of formaldehyde's effects. Specific information on endogenous concentrations of formaldehyde in human tissues, cytological effects, occupational health effects and mortality experience in humans must also be collected to fully understand formaldehyde's potential for carcinogenesis in humans. The significance of the carcinogenic effects in rats, however, dictates that formaldehyde should be kept at the lowest practical concentration in the workplace, in homes, and in ambient air.

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## TABLE 1

## INCIDENCE OF SQUAMOUS CELL CARCINOMA OF NASAL CAVITY: FORMALDEHYDE INHALATION FOR 24 MONTHS:[a]

| FORMALDEHYDE CONCENTRATION (ppm)[b] | NUMBER OF TUMORS/NASAL CAVITIES EXAMINED | |
|---|---|---|
| | RAT | MOUSE |
| 0 | 0/232 (0%) | 0/223 (0%) |
| 2 | 0/236 (0%) | 0/214 (0%) |
| 6 | 2/235 (0.9%) | 0/218 (0%) |
| 15 | 103/232 (44.4%) | 2/225 (0.9%) |

a. 6 hours/day, 5 days/week. The study was initiated with 960 Fischer-344 rats and 960 B6C3F1 mice, evenly divided by sex into treatment groups.

b. Target concentrations. Actual average concentrations were 0, 2.0, 5.6, and 14.3 ppm.

## TABLE 2

## ADJUSTED INCIDENCE OF SQUAMOUS CELL CARCINOMA OF NASAL CAVITY: FORMALDEHYDE INHALATION FOR 24 MONTHS[a]

| FORMALDEHYDE CONCENTRATION (ppm)[b] | NUMBER OF TUMORS/ANIMALS AT RISK[c] RAT | MOUSE |
|---|---|---|
| 0 | 0/208 (0%) | 0/72 (0%) |
| 2 | 0/210 (0%) | 0/64 (0%) |
| 6 | 2/210 (1%) | 0/73 (0%) |
| 15 | 103/206 (50%) | 2/60 (3.3%) |

a. 6 hours/day, 5 days/week. The study was initiated with 960 Fischer-344 rats and 960 B6C3F1 mice, evenly divided by sex, into treatment groups.

b. Target concentrations. Actual average concentrations were 0, 2.0, 5.6, and 14.3 ppm.

c. Actual number of animals exposed to formaldehyde up to, and including, the interval when the first squamous cell carcinomas were found (months: 11 - 12 for rats; 23 - 24 for mice).

## TABLE 3

VIRTUALLY SAFE DOSES OF FORMALDEHYDE IN RATS FOR SELECTED EXCESS RISKS OF SQUAMOUS CELL CARCINOMA OF THE NASAL CAVITY PREDICTED FROM UNADJUSTED PROPORTIONS (TABLE 1) USING THE PROBIT, GAMMA MULTI-HIT LOGIT, WEIBULL, MULTI-STAGE, AND LINEAR EXTRAPOLATION MODELS.

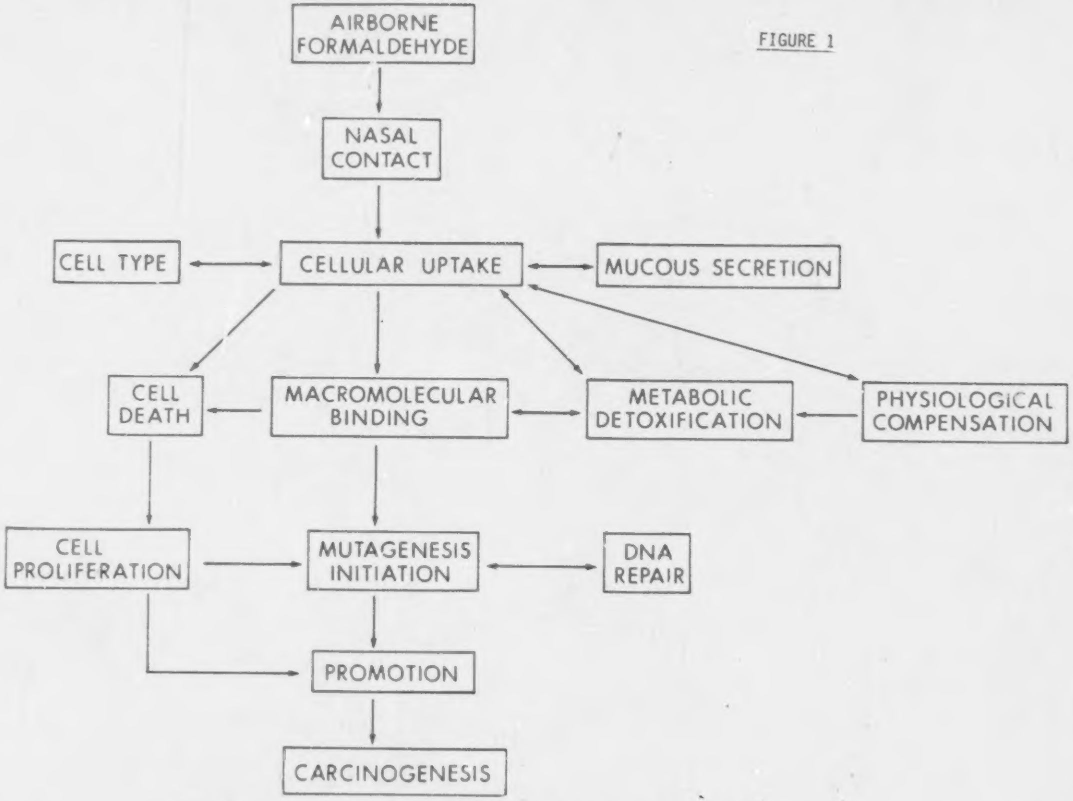
| | FORMALDEHYDE VIRTUALLY SAFE DOSE (PPM) | |
|---|---|---|
| MODEL | 1:1,000,000 | 1:100,000,000 |
| PROBIT | 2.08 | 1.46 |
| MULTI-HIT | 1.47 | 0.81 |
| LOGIT | 0.87 | 0.34 |
| WEIBULL | 0.76 | 0.28 |
| MULTI-STAGE | 0.66 | 0.21 |
| LINEAR | 0.00066 | 0.0000066 |

## TABLE 4

VIRTUALLY SAFE DOSES OF FORMALDEHYDE IN RATS FOR SELECTED EXCESS RISKS OF SQUAMOUS CELL CARCINOMA OF THE NASAL CAVITY PREDICTED FROM ADJUSTED PROPORTIONS (TABLE 2) USING THE PROBIT, GAMMA MULTI-HIT, LOGIT, WEIBULL, MULTI-STAGE, AND LINEAR EXTRAPOLATION MODELS.

| | FORMALDEHYDE VIRTUALLY SAFE DOSE (PPM) AT EXCESS RISK FACTORS | |
|---|---|---|
| MODEL | 1:1,000,000 | 1:100,000,000 |
| PROBIT | 2.14 | 1.52 |
| MULTI-HIT | 1.52 | 0.86 |
| LOGIT | 0.89 | 0.35 |
| WEIBULL | 0.76 | 0.28 |
| MULTI-STAGE | 0.65 | 0.21 |
| LINEAR | 0.00059 | 0.0000059 |

FIGURE 1


AIRBORNE FORMALDEHYDE
NASAL CONTACT
CELL TYPE
CELLULAR UPTAKE
MUCOUS SECRETION
CELL DEATH
MACROMOLECULAR BINDING
METABOLIC DETOXIFICATION
PHYSIOLOGICAL COMPENSATION
CELL PROLIFERATION
MUTAGENESIS INITIATION
DNA REPAIR
PROMOTION
CARCINOGENESIS

Conceptual model of various stages in the progression from the inhalation exposure of rats to formaldehyde to the development of squamous cell carcinoma in the nasal cavity.

Mr. **Gore**. Well, thank you very much. We are glad to have the statement. We will withhold questions until we have heard from Dr. Sielken.

Dr. **Sielken**. I want to thank the committee for allowing me to present material in what is obviously an unusual manner. Coming from an educational environment, I was not quite prepared for this.

Mr. **Gore**. You are going to present slides, are you? OK. That is fine.

We want to welcome the camera crew from the Formaldehyde Institute, also.

Go ahead, if the staff could get the lights for you. Is this the analysis that you presented at the Hernandez science court?

Dr. **Sielken**. Some parts of it are, and there are some parts that EPA had a chance to see but CPSC has not had a chance to see.

Mr. **Gore**. Has it been published?

Dr. **Sielken**. I have spoken at several meetings on this. There is no published paper in literature.

Mr. **Gore**. It has never been submitted for peer review?

Dr. **Sielken**. No.

Mr. **Gore**. Go ahead.

## STATEMENT OF DR. ROBERT L. SIELKEN, JR., TEXAS A&M UNIVERSITY

Dr. **Sielken**. From the research that I have been doing in this area of carcinogenic risk asssessment, several papers have been published but not this particular one.

To explain where I am coming from, Dr. Hartley, while he was alive, and myself, were involved in the initiation of models incoroporating the time to a carcinogenic response into risk assessment. This was a departure from the quantal response-type analyses that had preceded us. These models were developed during the years 1973 to 1978, and these were done under contracts with the Food and Drug Administration and the National Center for Toxilogical Research. This research was extended recently with the support of the National Institutes of Health.

In particular, I have been responsible for developing computer software as well as statistical procedures implementing models incorporating time to response. This software has been supplied rather widely to research institutes, industrial companies, and to Government agencies; in particular the Food and Drug Administration and EPA have both asked for this type of software as well as expository material explaining it.

It was in connection with this software development that I was asked by the Formaldehyde Institute to attend what is being called today the science court, and I was glad to do so. I do not get a chance to come to Washington very often to explain what I am doing, which is normally not readable to most, so I was happy to come and serve as an expert on these statistical models and procedures for low dose risk extrapolation, not as an expert on carcinogenesis as such but as an expert on the properties and procedures used to analyze such data.

I was asked specifically to do two things: I was asked to explain how the exposure time, the length of time at which an animal or a man would be subject to risk, that was part of the CIIT study might be included in the risk assessment. The other thing I was asked to do was to review the procedures that EPA had been using, as far as their sensitivity.

Now I am sorry Dr. Crump had to leave to catch a plane because he and I have both been working in this area and he was the developer of the multistage model. He and I both participated in several conferences together.

Mr. GORE. Without objection, we will hold the record open for Dr. Crump's comments on this, since you have worked with him.

Dr. SIELKEN. Yes; as a matter of fact, I told him that I would send him what I had and ask for his comments as well.

The multistage model is in general a good model in some situations. The thing that I have become aware of is that it does suffer from some limitations when there is no direct experimental evidence of carcinogenic risk at the low-dose levels. Therefore, it is a good procedure in some situations and in some other situations you should be aware of its limitations. That, as a statistician, was what I was trying to show the EPA. Let me give you two examples of these limitations.

The first refers to the number of dose levels that were actually in the CIIT experiment. The number of dose levels actually limited the ability of the multistage model to reflect low-dose nonlinearity (the flatness) in the formaldehyde dose response relationship.

Let me give you an example which shows what that restriction in the number of doses can do to the risk assessment. I showed a similar slide to this at the EPA meeting.

In the original analysis shown in brown there were four dose levels, and these were the numbers of animals responding out of the number available if you ignore the animals that were sacrificed early. Therefore, in brown you had 0 out of 160, 0 out of 160, 3 out of 160, and 87 out of 160 at 0, 2.1, 5.6, and 14.1 ppm respectively. Suppose you take that 0 out of 160 that occurred at the dose level 2.1 and you just split it up into almost identical dose levels. Mechanically this allows the multistage model to use one degree higher in the fitted model. Therefore, a rather simple, arbitrary nonchange in the data itself allows the model to do something differently than it would if it was restricted by the number of dose levels.

In particular, if you just create this extra dose level and thereby give that multistage model an extra degree of freedom, the risk level changes from $0.9 \times 10^{-7}$ to $0.5 \times 10^{-9}$; so the fact that there were only four dose levels instead of five forced the risk assessment to be 180 times larger than it would be if there were in fact five risk levels instead of four. This is what I meant by a limitation due to the number of dose levels available.

This limitation does not continue if you take the two dose levels at around 2 and split it up into three so that you have six dose levels. At six dose levels the risk does not change much at all. It goes from $0.5 \times 10^{-9}$ to $0.4 \times 10^{-9}$; so you just need to give the model a little more freedom not a lot.

Mr. GORE. Excuse me, Dr. Sielken. Are you talking about rats?

Dr. **Sielken**. Yes. This is the data as it appears in the CPSC Murray Cohn paper.

Mr. **Gore**. Thank you. If you could move it along and maybe summarize some portions of it that are not critical to your presentation, we would appreciate it.

Dr. **Sielken**. I will try to do that.

Mr. **Gore**. That is because of the lateness of the hour only, and we appreciate it.

Dr. **Sielken**. I have a plane at 5:55, too.

Mr. **Gore**. OK.

Dr. **Sielken**. The other thing that I wanted to be sure to point out to this body here as well as to the EPA was about the 95 percent confidence limits that are given by Global 79, and the fact that these tend to grossly overestimate the carcinogenic risk in the type of situation that the formaldehyde data represents. Global 79 is the computer program used to analyze the multistage model.

Not being statisticians, most people feel that there is only one way to do confidence limits. They have a tendency to consider confidence limits as point estimates or to use them as if they were really estimates of risk.

In a recent submission to Chairwoman Steorts of the CPSC I made the following argument: Unless the true dose-response relationship is linear, as shown in brown, all the way from 0 out to 5.6, unless the linearity really extended that far, the ratio between the upper confidence limits and the true risk could easily exceed 100. Therefore, unless that linearity which is part of a lot of the modeling argument, unless that linearity extends a long way out into the data, the upper confidence limit tends to be grossly overestimate the actual risk.

Let me just indicate the importance of the realization that upper confidence limits really give you a big upper bound on risk. In order to indicate the difference between the maximum likelihood estimates in purple, that is the best-fit-to-the-data estimates in purple, and the upper confidence limits shown in brown, the ratios are shown in black—in other words, how much bigger the upper confidence limit on risk is than the true risk. For the level 0.07, which was the average in the CPSC exposure information, you are talking about a ratio of about 1,000 or 824. Therefore, the fact that you are using upper confidence limits really does have a tremendous impact on the risk assessment.

I was asked to give my opinion of what I really felt the carcinogenic risk was, based upon the statistics, and my answer to that is here, taking into account first the limitations of the multistage model in this type of situation where there is no direct experimental evidence for the low-risk levels, and taking into account its limitations in that situation as well as the empirical behavior of the best estimates and the 95 percent upper confidence limits, the cancer risk due to inhalation of formaldehyde released from UFFI is probably at least 100 times smaller than the quoted 51 in 1 million. That is less than one-half in 1 million.

This is the type of information that I presented to the EPA at the science court. I did not have an opportunity until very late to submit any remarks like this to the CPSC, simply because I am not aware of everything that goes on in Washington.

Thank you for your indulgence.

Mr. **Gore**. Thank you very much. We appreciate that.

Dr. Schwartz, we are delighted to have you here as well. We appreciate your patience as the last witness.

We would like you to provide those transparencies for the record, Dr. Sielken, if you would.

Dr. **Sielken**. Certainly.

Mr. **Gore**. Fine. In view of the fact that we have not been able to analyze your figures, without objection I would like to hold the record open for an analysis of your statement for the record.

Dr. Schwartz, thank you for your patience. Go ahead.

## STATEMENT OF DR. SORELL SCHWARTZ, GEORGETOWN UNIVERSITY

Dr. **Schwartz**. Mr. Chairman, I thank you for your patience.

My curriculum vitae has been submitted, so I will not go through my qualifications.

Mr. **Gore**. We have it, and let me stipulate for the record, it is very impressive and we are truly delighted to hear from you.

Dr. **Schwartz**. I am professor of pharmacology at Georgetown University and will just say that I received my Ph. D. in pharmacology from the Medical College of Virginia which the chairman knows is in Richmond, Tenn. [Laughter.]

I will foreshadow my comments by saying that I am not here to tell you that formaldehyde is safe nor will I tell you that it is unsafe. I am not going to raise the question as to whether formaldehyde is or is not a carcinogen. It is in fact demonstrated to be an animal carcinogen, and my own personal philosophy is that if something is demonstrated to be an animal carcinogen, irrespective of all theoretical considerations, it must be, at this particular time, for reasons of prudence, to be considered as a human carcinogen.

The question is not whether it is a human carcinogen but whether it presents an unacceptable risk. As we know, safety is, in fact, acceptable risk or not unreasonable risk, except under the Dulaney clause. The question is: What is acceptable or a not unreasonable risk? Who determines acceptability and with what information?

A now-famous comment was made by former Senator Edmund Muskie in which he expressed the belief that what the country needed was more one-armed scientists. He was referring, of course, to the uncertainties in determining environmental health effects which cause scientists to say, "on the one hand," but "on the other hand." The facts are that the uncertainties in assessing risks represent reality and, more importantly, it is imperative that these uncertainties become an integral part of the decision as to the acceptability of the assessed risk.

Most important of all is that it is not the responsibility of the scientist to determine the acceptability of the risk. It is a political responsibility. The only way that designated public officials can deal with that responsibility is to demand full explanation, education, and clarification.

There is a question now before you concerning formaldehyde and as to what information should be used in assessing the risk or evaluating the risk. Of the epidemiology data, it has been said, "It is too insensitive." We have spoken of risk assessment or risk analysis. Part of this is what we call low-level risk analysis, the use of mathematical models for estimating low-level risk from low-dose exposure.

Unfortunately, there are one-armed scientists who rely on such estimates as the almost sole criteria for assessing risk and advising us as to the acceptability of risk. An editorial by Robert B. Cumming, of Oak Ridge National Laboratory, which appeared in "Risk Analysis," a publication of the Society for Risk Analysis, about 1 year ago, was entitled "The Urge To Shout."

In referring to the disagreements among members of the risk assessment community, he states,

> Risk analysis is a new and a rapidly expanding field. As such, it has many new recruits and there is much jostling for position. As in any new field, the leadership is not clear and recognition is necessary not only to establish one's credentials but also to compete for research support in an atmosphere where science in general is facing shrinking financial resources. It is important, therefore, for one's point of view to be heard above the din. Any evidence that is not being heard or considered is a powerful stimulus to the urge to shout. Estimates of risk are currently made with great uncertainty and considerable imprecision. There does not exist a large body of generally accepted methodology for risk measurement and risk calculation. Thus, the field is wide open for the development of strongly held conflicting opinions. The underlying social philosophies in areas to which risk analysis is applied generate deeply held opnions and highly polarized positions. Although risk may be only a minor consideration in the decisionmaking process, when risk analysis is used to support a particular technological option, it generates shock waves which unsettle underlying social attitudes and challenge deeply entrenched beliefs. Such challenge leads quite naturally to questions about methodology, motives, and competence of the risk assessor who had the temerity to produce such results. Given the primitive state of the art, there is always ample room for such questions to arise and once they have arisen, there is a strong motivation to make sure they are generally heard. To a large extent, what people hear is tempered by what they believe and not the reverse. New information must pass through a filter which screens out elements inconsistent or threatening to the mental structure which has already been built up. Thus, individuals have both a receiver and transmitter tuned to a particular wavelength, and when they are trying to communicate with each other on different wavelengths, they talk past rather than to each other. When one realizes that his message is not being heard, it strongly stimulates the urge to shout. This has the immediate effect of producing more sound while producing less communications. The principal actors in these debates have their own constituencies which are already tuned to their message. Shouting may be part of putting on a good show for one's audience but it has more than entertainment value in this setting. It is a constant reminder that the battle against the heathen is still being sought.

The individual who believes that high-dose exposure gives an accurate estimate of low-dose effects to the exclusion of the consideration of other data is naive, a zealot, or uninformed. There is no more reason to reject epidemiology data because of sensitivity problems than there is to reject quantitative risk estimates because of uncertainty. All factors must be brought into the acceptability equation. Cost must be considered, the means of use.

Formaldehyde is a case in point. We have here conflicting data. We have heard conflicting data and opinions here today. How serious a consideration has been given to the benefits of formaldehyde? What is the cost of being without formaldehyde? What are the health risks of substitutes for formaldehyde? What are the health risks of not having formaldehyde? None of this has been considered in determining acceptability of risk.

Compare this with the decision by the CPSC not only to ban formaldehyde but in public press conference to imply, certainly as I read them in the Washington Post, that homes with formaldehyde foam are a health hazard. There is not a shred of data which suggests that most of the homes, except where installation errors have been made, are under a risk, yet there are people who fear cancer from their homes who cannot afford to or do not want to move out of their homes, who have reduced values of their homes. The extraordinary cost of the likely unnecessary removal of the insulation is being considered. This is all part of determining acceptability of risk.

Mr. GORE. Excuse me, Dr. Schwartz. You are not saying that the cost figures should be taken into account in the initial stage of determining the health risk, are you?

Dr. SCHWARTZ. I am not saying that cost figures should be taken into account at all in determining the health risk. I am saying the cost figures should be taken into account in determining the acceptability of risk, and to foreshadow what I am saying——

Mr. GORE. That is a completely different subject from the one we are addressing here today.

Dr. SCHWARTZ. Well, I have a few more comments in my statement and I think I will attend to that in my closing comment, if that is OK, Mr. Chairman.

The shouting is real, I have been and continue to advise Government and industry. It seems at times when one represents the tighter regulatory position it is good and wholesome. It is a heroic defense of the Nation's health against the ledger minded industrialists. When one works with the industry, one is bordering on intellectual prostitution or, as one former agency administrator said to a colleague of mine, a father of six children, after he had testified in favor of an industry position, "You must do this because you have a lot of kids in college."

Well, I have worked with the chemical industry and with the agriculture industry, and I have never seen anything from their material safety people other than concern for health. The implications today that the Todhunter memo looked like it came from an industry representative, to me makes a pejorative presumption that industry science cannot be trusted, that safety is subverted in the interest of profit. This is an incredible indictment and, as I have stated, from my own observations to be except in rare instances, unsupportable.

We return to the matter of what is significant or unreasonable risk, and I suggest that is the question that we should deal with. I believe in the final analysis this is what the Todhunter memo dealt with, not the level of risk but the acceptability of that risk under 4(f) at that particular time.

I would like to close with two statements. One is from the President's panel on chemicals and health of the President's Science Advisory Committee from 1972, and I quote:

> If the public is exposed to too many vivid accounts of nonexistent or very minor threats to health, its attention will be misdirected, its priorities will be confused, and its responsiveness to important messages will be decreased.

Finally, from Senator Kennedy, I quote:

> We must begin educating the public to the reality that there is no such thing as absolute safety. Regulation can never completely and totally protect the public. Large segments of the American public already accept this fact but it is time for

persons in positions of leadership to strengthen this understanding with a more candid discussion of the limitations of regulation.

Again, Mr. Chairman, I thank you for your patience.

Mr. GORE. Well, I find your statement a little puzzling, Dr. Schwartz. I do not know quite what you are getting at. Do you accept the scientific judgments in the Todhunter February 10 memo? Do you think it is good science?

Dr. SCHWARTZ. I have not read anything in the Todhunter memo——

Mr. GORE. Oh——

Dr. SCHWARTZ. No, no. I have read the Todhunter memo. However, I have never read anything in the Todhunter memo which to me involves science. I think what Dr. Todhunter did was act as a nonscientist, and that is to make a determination whether the risk as presented by the data was significant enough to be unacceptable under 4(f). I do not read it as Dr. Todhunter saying that formaldehyde was safe, that formaldehyde did not have to be regulated, only that it was not necessary at that particular time to regulate or to act on formaldehyde within 180 days. I assume that was done based on the likely exposure levels. It is not as if the population was being exposed to levels of 15 ppm. I think consideration of what the likely exposure levels were in houses or from particleboard or from foam were not enough to engender concern under the section of the act he was working with.

Mr. GORE. I just do not understand your response. The question was, Do you agree with the scientific judgments in the document? You say it is your view that he was writing it as a nonscientist. That is a little odd. He is the chief scientist responsible for the EPA toxics program and the agency published this document and released it to the public as the scientific justification for the decision. It discusses scientific judgments throughout. How can you say that it is written as a nonscientist, as a nonscientific document?

Dr. SCHWARTZ. I am saying that what Dr. Todhunter did when he reviewed the document, in my mind, was reviewing the document from the viewpoint of the acceptability of the risk.

Mr. GORE. What about all the discussions of the scientific questions in that document?

Dr. SCHWARTZ. I agree all the discussions were there. I do not agree with all of his science, if that is what you mean.

Mr. GORE. That is what I am asking. Do you disagree with the scientific judgments in that document?

Dr. SCHWARTZ. No, I said I did not agree with all of them, nor do I agree with——

Mr. GORE. Which ones do you disagree with?

Dr. SCHWARTZ. Well, I disagree with the emphasis which he placed on the risk assessment information.

Mr. GORE. What about his statements on epidemiology?

Dr. SCHWARTZ. I do not favor the idea that negative epidemiologic data signifies negative human effect. You cannot prove a negative.

Mr. GORE. OK. You disagree with that, too. What about the free form formaldehyde?

Dr. SCHWARTZ. The endogenous levels, you mean? Are you referring to the endogenous levels?

Mr. GORE. Yes.

Dr. SCHWARTZ. Well, from what I heard from him today I do not disagree.

Mr. GORE. Do you disagree or agree with the statements in the Todhunter memo on free form formaldehyde?

Dr. SCHWARTZ. If they were meant as he explained them today——

Mr. GORE. No, the statements in the memo.

Dr. SCHWARTZ. Can you give me a particular quote that you are referring to?

Mr. GORE. Yes. Hold on a second.

"Normal endogenous tissue levels of formaldehyde produced by metabolism range from 3 to 12 nanograms per gram of tissue."—3 to 12 parts per million—"Much of this appears to be bound up as adducts to glutathione, tetrahydrofolate, and proteins. From 10 percent to 40 percent of the total tissue formaldehyde appears to exist as free formaldehyde."

Dr. SCHWARTZ. I had no trouble with that from a mass action point of view. In other words, the fact that formaldehyde is in an equilibrium with——

Mr. GORE. Where do the 10-percent to 40-percent figures come from? Have you ever seen a scientific study that——

Dr. SCHWARTZ. No; I assume that he was referring to what is common in the body as "associated and dissociated" reaction. In other words, tetrahydrofolate is the active form of formaldehyde and it has what is referred to as an equilibrium constant, so——

Mr. GORE. Can that interact with DNA?

Dr. SCHWARTZ. Tetrahydrofolate, with formaldehyde attached, is responsible for the body's manufacture of DNA. In fact, that is why I was rather surprised when Dr. Griesemer expressed his concern about endogenous formaldehyde levels. Those endogenous formaldehyde levels are necessary for the synthesis of DNA, and also those endogenous formaldehyde levels are a result of the major drug metabolism routes in the body.

Mr. GORE. What about a statement that cancers are probably caused by the irritation, the rat nasal cancers probably being caused by the irritation?

Dr. SCHWARTZ. I think it is another view but I would not accept it as a fact.

Mr. GORE. Therefore, you reject that scientific judgment also.

Dr. SCHWARTZ. I reject it as a conclusion, yes. I accept it as a possibility but not as a conclusion.

Mr. GORE. Well, there are a number of serious scientific misjudgments, in your view then, in the Todhunter memo.

Dr. SCHWARTZ. I did not mean to imply that I agreed with the Todhunter memo from the viewpoint of all his science. I agreed with it from the viewpoint of his determination of acceptability.

Mr. GORE. I see. However, there is no information on exposure in there, is there, in the memo?

Dr. SCHWARTZ. The exposure of the human population?

Mr. GORE. Yes.

Dr. SCHWARTZ. No, not that I can recall.

Mr. GORE. Therefore, how do you come up with your conclusions on acceptability, then?

Dr. SCHWARTZ. I think he stated—well, I know what the exposures are. That is why. In other words——

Mr. GORE. Do you know from the court case where you were employed by the producer of formaldehyde?

Dr. SCHWARTZ. Yes, not producer of formaldehyde but producer of tripolymer foam.

Mr. GORE. OK. Thank you very much.

Dr. Gibson, you say, "Cell injury and cell proliferation was correlated with formaldehyde carcinogenesis." Now, correlation does not necessary mean cause, correct?

Dr. GIBSON. Yes, that is right. Correlation does not mean cause.

Mr. GORE. Nor does it mean unnecessary prerequisite, does it?

Dr. GIBSON. No, that is quite true.

Mr. GORE. How accepted is the idea that the interaction of formaldehyde with DNA is by the route of irritation?

Dr. GIBSON. The question is, How well accepted is the idea that formaldehyde's interactions with DNA is related to irritation?

Mr. GORE. Is by the irritation route.

Dr. GIBSON. I do not know of anyone who relates those two phenomena.

Mr. GORE. Dr. Todhunter appears to believe that. Now maybe I am misrepresenting his view but the memo appears to indicate a view that the irritation necessarily preceded the cancer in the rat study, and that the inference he drew was that it was a causal factor.

Dr. GIBSON. May I address that, Mr. Chairman?

Mr. GORE. Yes.

Dr. GIBSON. Just from the standpoint of our own work and without reference to Dr. Todhunter's interpretation, in our work we have found that there is a correlation between the concentrations of formaldehyde that cause cancer and those that produce severe cell injury and an increase in cell proliferation. What we mean is that because the cells are being injured and dying there is an adaptive response for replacement of injured and dead cells, and that adaptive response is an increase in the cell replication rate in the stem cells, the precursor cells underlying the nasal mucosa.

Mr. GORE. However, you are just saying that there is a correlation. You are not saying that without irritation leading to cell injury and proliferation, cancer cannot develop.

Dr. GIBSON. No, I am not saying that.

Mr. GORE. I see. All right. Well, that assumption seems to be built into a part of the Todhunter memo.

Let me move to page 3 of your statement. You say: "Two rats with squamous cell carcinomas in the nasal cavities were found following exposure to 6 parts per million formaldehyde for 24 months." In 24 months, 50 percent of those rats exposed to 15 ppm developed squamous cell carcinomas. Didn't it seem odd that there would be such a great drop, in effect, between 6 and 15 parts per million formaldehyde?

Dr. GIBSON. No, it does not seem odd at all. The dose-response relationship is a well-known biological phenomenon. It is the basis for all of the pharmacologic activity of drugs that we use, as well as a well-known principle in toxicology. We have to keep in mind the concept that different chemicals will produce a different slope in the dose-response curve, and in the absence of information about the slope you simply would not be surprised by such a finding.

Mr. GORE. Yes, but the drop was far greater than the drop in the exposure, significantly greater.

Dr. GIBSON. I do not understand the situation that way at all. What is really the question? What is the response between 6 and 15 is what you are getting at, and——

Mr. GORE. Yes, that is right, and there was a tremendous drop in the effect that is far greater than one would expect from the drop in the exposure level.

Dr. GIBSON. Not at all, sir, because we do not have any information about what the slope of the dose-response curve is. There is never going to be a defined slope for a dose-response. It is a property of each and every individual chemical.

Mr. GORE. Well, if there are no studies indicating that, have any been done? Have any been started?

Dr. GIBSON. The way that CIIT has proceeded with this problem was to conduct a preliminary study in rats and mice, and this study was of 90 days duration, where animals were exposed daily for 6 hours. The concentrations that were used in that study ranged up to 40 ppm and down to 12.5 ppm. In that study the concentration of 40 was far too high to allow the survival of the animals. Consequently, we did not get a good indication of what the dose-response would be but every toxicological study is designed to produce information. Where the highest concentration produces a definitive toxicologic effect, ideally the intermediate concentration would produce some sort of an intermediate effect while the lowest concentration may produce a minimal or no effect. Our study did follow that general goal in the results.

Mr. GORE. You say, "or no effect." It did produce an effect, didn't it?

Dr. GIBSON. Oh, yes. In our study there were effects at 2 ppm. The effects that were seen, however, could be interpreted by scientists in different ways. One interpretation is that the changes that are observed are adaptive responses. Another interpretation is that the adaptive response is an adverse effect.

Mr. GORE. Now there were two nasal carcinomas in the 6 ppm group, correct?

Dr. GIBSON. There were two animals with squamous cell carcinoma; yes.

Mr. GORE. Do you think that was insignificant?

Dr. GIBSON. I have never said that, though.

Mr. GORE. However, Dr. Todhunter said today that CIIT had described that as "statistically insignificant."

Dr. GIBSON. Well, sir, there is a difference, as we heard earlier, between statistical significance and biological significance. The statistical procedures that were used by CIIT are exactly the statistical procedures used by the National Cancer Institute in the analysis of their bioassays. In that analysis, the interpretation that we came to would be identical to that that the National Cancer Institute would have come to using the same methodology.

Mr. GORE. Therefore, to describe it as "statistically insignificant" really obscures the fact that it is quite significant because these nasal carcinomas have almost a zero base line. They are very rare.

The occurrence of two carcinomas in the 6 ppm group is significant.

Dr. Schwartz. Could I respond to that, Mr. Chairman?

Mr. Gore. Yes. Let me ask Dr. Gibson first.

Dr. Gibson. Yes, I would be happy to respond to that. The statistical procedures that are in use are to help us make decisions about whether what we see is occurring by chance or not. Even though the tumors at 6 ppm were not statistically significant, they were the same type of tumor that was seen at 15 ppm. Consequently, in the risk assessments that we have done and all of our research thinking, we have never thought anything other than that these are of importance in understanding the effects.

Now statistical significance, though, has to be paid attention to in making administrative decisions about a set of data. There were no tumors in the 2 ppm group and no tumors in the control groups, as you corrently pointed out.

Mr. Gore. Yes.

Dr. Schwartz?

Dr. Schwartz. This situation has a direct analogy to the cyclamate situation, and that is that a review of the cyclamate data in the recent court case by the California canners and growers has shown a high level of probability that in the cyclamate-saccharin mixture that was given to these rats, there is a serious question as to whether cyclamate was carcinogenic.

One of the situations that occurred was that bladder tumors in rats were so rare that it was considered that the development of any bladder tumor in a rat was significant because of their rarity but, in retrospect, one of the reasons that they were rare was because nobody ever looked for them. Since the cyclamate study, when we have become attuned to bladder cancer, all of a sudden now that we look for bladder tumors we find more of them in control animals, and the control incidence of bladder cancers has increased. A similar situation "may," I say may very well exist in nasal tumors where traditionally in the bioassay studies a single section is taken through the nasal cavity so that there is no organized search for nasal cavity tumors. Perhaps because of this study we will now start looking for nasal cavity tumors and may have a similar situation where the background will arise.

I am not claiming that your presumption is incorrect but I am saying that there is a possibility that the reason that they are low incidence is because they are not being looked for.

Mr. Gore. An interesting hypothesis, Dr. Schwartz.

Dr. Gibson, do you maintain that the nasal tissue is the only site where cancer from formaldehyde can develop?

Dr. Gibson. The only evidence that I have at my disposal indicates that that is the only site.

Mr. Gore. In humans?

Dr. Gibson. I have no information about that, sir.

Mr. Gore. Is that a reasonable assumption?

Dr. Gibson. That cancer would arise at other sites in humans due to formaldehyde exposure?

Mr. Gore. Is it reasonable to assume that nasal tissue is the only site where cancer from formaldehyde can develop in humans?

Dr. Gibson. I really do not have all the information I would need to make that judgment but, based on what I do know from the animal studies, we do know that the tumors arose only in the nasal tissue. Furthermore, we do know that most of the formaldehyde that is inhaled is retained in the nasal tissue.

What we do observe is that a vast majority of that formaldehyde is metabolized readily to carbon dioxide. Some appears in the urine and the rest appears to be incorporated into normal constituents of cells. It is unclear to me how formaldehyde would produce tumors at distant sites but you cannot rule that out.

Mr. Gore. Well, it penetrates deeper into the body than just the upper nasal area, does it not?

Dr. Gibson. We have evidence that formaldehyde as formaldehyde may penetrate the nasal epitheliums and into the tracheal tissue. We do not have any evidence that it gets any further than that as formaldehyde. However, the carbon atom associated with the formaldehyde is spread throughout the body, incorporate into normal nucleic acids, proteins, lipids, amino acids, and the like.

Mr. Gore. Therefore, you would limit it to the nasal area and the tracheal area?

Dr. Gibson. Well, I think the situation in jumping from the obligatory nose breathers like rats and mice to people has to take into account that people can be mouth breathers, and so I think my major concern would be with the upper respiratory tract.

Mr. Gore. Therefore, you would look for cancers in the mouth as well?

Dr. Gibson. Yes, I would.

Mr. Gore. What about the larynx?

Dr. Gibson. Yes.

Mr. Gore. Throat?

Dr. Gibson. Yes.

Mr. Gore. Lung?

Dr. Gibson. No.

Mr. Gore. Why not?

Dr. Gibson. Well, the evidence—and I am going to restrict my comments only to inhaled formaldehyde as the gas—the evidence that formaldehyde as formaldehyde reaches the lung is such that we just do not have any evidence that it does reach it in that form. I suppose there is a case that one could consider where formaldehyde might adhere to some kind of a foreign body and be carried into the lung but I have no information whatsoever about that, sir.

Mr. Gore. Thank you.

Dr. Sielken, Dr. Todhunter used median exposures in order to compute risks. Does the selection of median exposures overstate or understate risks compared to using arithmetic mean estimates of exposures?

Dr. Sielken. Actually, it can be either, depending upon the importance of time in the response relationship. If there is a period of time that must transpire before something happens, then using the median dose would overestimate the risk. If the reaction can take place immediately then it tends to underestimate the risk, so it can be either way.

Mr. Gore. We are going to excuse Dr. Gibson, who has to catch a flight, and we are going to finish this up very quickly.

All right. Would you be willing to answer additional questions for the record, doctor?

Dr. SIELKEN. Certainly.

Mr. GORE. All right. Fine. We want to clarify that for the record. In the specific context of the technical documents at EPA—you are familiar with those documents, aren't you? In that case, did the selection of median exposures overstate or understate risks, compared to the use of arithmetic means?

Dr. SIELKEN. To the best of my knowledge, I felt from my modeling of the time-to-response information based upon approximate CIIT data that it probably would overestimate the risk but you are out on the boundaries of what we know in statistical procedures.

Mr. GORE. We will have additional questions for the record on that subject. Using a linear, no-threshold approach, should one use the mean or the median?

Dr. SIELKEN. Let me answer it this way. I tried to look at that and could not reach a firm conclusion. But relative to using any number in the range of what the CPSC, for example, estimated to be the exposure level from 1 year to 9 years, using any of those numbers did not make that much difference relative to the size of the difference that you got if you went from best estimate to upper confidence limit. You are talking about several orders of magnitude on one side and nitpicking over a couple of factors, like multiplying by 2, for using a mean or a median, so——

Mr. GORE. Can you—excuse me, go ahead.

Dr. SIELKEN. I was just saying that relatively there is not much difference there compared to the difference between using the best estimate and the upper confidence limit.

Mr. GORE. Can you provide your time-to-tumor analysis for the record?

Dr. SIELKEN. Yes. There have been several. I have not published anything.

Mr. GORE. On formaldehyde.

Dr. SIELKEN. I am not sure how I should answer that. That is in the research process. Certainly I will be glad to supply the——

Mr. GORE. Well, you presented some statements related to it, did you not?

Dr. SIELKEN. No. I indicated that my specialty and background is in the time-to-response information. I did not include that time-to-response information specifically in my estimates of risk that I showed.

Mr. GORE. I see. Well, could you provide it for the record?

Dr. SIELKEN. Certainly.

Mr. GORE. Fine. OK. Is that being done for the Formaldehyde Institute, incidentally?

Dr. SIELKEN. No. The time-to-tumor analysis procedure it was actually being done for the National Institutes of Health. The application of that procedure to the CIIT date is currently being done for the Formaldehyde Institute.

Mr. GORE. All right. Thank you very much.

Now was your analysis submitted to the CPSC used by the CPSC?

Dr. SIELKEN. They expressed interest in it and interest in learning more about the ideas that I presented. They were presented close to the deadline, and in speaking with a couple of the individuals here today, they indicated that they had seen it and read it, but I think it was late in their process, so I doubt if it was incorporated. I do not know the answer to your question, specifically.

Mr. GORE. I would like to recognize counsel for the minority.

Mr. CLEMENT. Dr. Sielken, I would like just a couple of clarifications, if I could. When we attempt to quantify risk, isn't it true that risk is actually a function of time of exposure times some quantity that you express the danger involved in?

Dr. SIELKEN. You can express the probability of response as a function of both dose and time, and that is the way we have tried to model it.

Mr. CLEMENT. On your slides you were showing that you thought that the actual danger, instead of 51 in 1 million, was 0.05 in a million. Can you recall that?

Dr. SIELKEN. That was 0.5 in 1 million, half a million.

Mr. CLEMENT. How many parts per million does that represent in formaldehyde?

Dr. SIELKEN. That was the risk level that I felt applied to an average of 0.07 ppm.

Mr. CLEMENT. That was 0.07? All right.

Dr. SIELKEN. That was the average that CPSC used.

Mr. CLEMENT. One other question: The chairman asked you a moment ago about using a linear, no-threshold approach. Let me ask you, based on the data that you have seen, the observed data, does the linear, no-threshold approach seem reasonable to use? Does it really fit the observed data as well as a nonlinear, threshold approach does?

Dr. SIELKEN. That was my point about confidence limits. I gave a recent example for some people that were laymen to say that you could bound Reggie Jackson's batting average by 1,000 and, for sure, that would be an upper confidence limit but it is not a point estimate. I really feel the same way about the upper confidence limit for risk. It indicates a range but it is indicating a wide range and not a very probable range.

Mr. CLEMENT. I thank you.

Dr. Schwartz, a final question for you, if I could: Based on everything you have heard here today, do you have any question that it is reasonable to reach the conclusion that formaldehyde as it applies to the general public does not present a significant risk at this time?

Dr. SCHWARTZ. I think we have a triple negative in there.

Mr. CLEMENT. I am sorry. I was not an English major.

Dr. SCHWARTZ. Well, you are asking me whether I think it presents a signficant risk, and I have to go by a very, very strong philosophical bend which I have, and that is, I will tell you that I do not think it presents at this time a significant risk to the population if the formaldehyde level is kept at below 0.1 ppm. However, I do not think it is my job to determine whether the risk is significant or not.

Mr. GORE. If counsel would yield, you said 0.1 ppm?

Dr. SCHWARTZ. Yes, sir.

Mr. GORE. Well, some of the exposure levels are much higher than that.

Dr. SCHWARTZ. I said that I am comfortable below 0.1 ppm.

Mr. GORE. I see. Therefore, if the exposure levels are higher than that, then you think it is a significant risk?

Dr. SCHWARTZ. No. There is a difference between saying that I am comfortable below and uncomfortable above. I am not trying to twist the words around.

If, for example, you said, "Suppose it was 0.15?" No. "Suppose it was 0.5?"

Mr. GORE. What about 1?

Dr. SCHWARTZ. One? I do not consider 1, a lifetime exposure of 1, as being acceptable to me.

Mr. GORE. Well, that is very interesting. The OSHA level is 3.

Dr. SCHWARTZ. That is occupational exposure. That is different. I am talking about a 24-hour-a-day, 7-day-a-week exposure. On the other hand, based on the studies of the CIIT, I think the OSHA standard probably needs reexamination.

Mr. GORE. Very interesting.

Excuse me for trespassing on your time.

Mr. CLEMENT. Mr. Chairman, I was about to be very complimentary and I am not sure that after that I want to be. [Laughter.]

I would like the record to reflect, for those of you who have sat through this for so long, the rules of this committee do not require that the chairman allow the staff to participate. On this subcommittee we have a difficulty in that we have very limited numbers of minority members, and I am the minority staff. As you have been able to see today, the majority outnumbers us significantly.

The gentleman from Tennessee is truly a gentleman and has been most courteous in allowing me to participate, and I would like to say thank you, Mr. Chairman.

Mr. GORE. Thank you. You are most welcome.

I would like to thank our witnesses who have come on short notice. We appreciate the testimony you have provided here today. The hearing is adjourned.

[Whereupon, at 5:20 p.m., the committee recessed, to reconvene at the call of the Chair.]

# APPENDIX 1

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 10 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Data Available to the Administrator Concerning Formaldehyde and di(2-ethylhexyl) Phthalate (DEHP)

FROM: John A. Todhunter, Ph.D. John A. Todhunter PhD
Assistant Administrator
for Pesticides and Toxic Substances (TS-788)

TO: Anne M. Gorsuch
The Administrator (A-100)

THRU: John W. Hernandez, Ph.D.
Deputy Administrator (A-101)

## Summary

At your direction I have reviewed the materials prepared by the Office of Toxic Substances in regard to formaldehyde and DEHP. I have also reviewed the materials prepared early in 1981 by OTS which were appended to a letter from NRDC, dated September 4, 1981. This memorandum is a statement of my professional conclusions and policy recommendations regarding the documents reviewed. In summary: I find that I concur with the current recommendations of OTS that formaldehyde and DEHP ought not be considered under section 4(f) and that the preliminary drafts relied on by NRDC in their letter to you were incomplete and flawed.

## Technical and Policy Issues Related to Section 4(f)

The Toxic Substances Control Act (TSCA) was enacted by Congress to protect human beings and the environment from those chemical substances and mixtures whose manufacture, processing, distribution in commerce, use, or disposal pose unreasonable risks of injury. One of the provisions of the Act is Section 4(f), which states that:

> Upon receipt of 1) any test data required to be submitted under this Act, or 2) any other information available to the Administrator, which indicates to the Administrator that there may be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant

> risk of serious or widespread harm to human beings from cancer, gene mutations, or birth defects, the Administrator shall, within the 180-day period beginning on the date of the receipt of such data or information, initiate appropriate action under section 5, 6, or 7 to prevent or reduce to a sufficient extent such risk or publish in the FEDERAL REGISTER a finding that such risk is not unreasonable. For good cause shown the Administrator may extend such period for an additional period of not more than 90 days. The Administrator shall publish in the FEDERAL REGISTER notice of any such extension and the reasons therefor.

The purpose of section 4(f) is to identify certain chemical substances or mixtures as high priority candidates for regulatory action and establish a deadline for acting to regulate such substances as are found to meet section 4(f) criteria. A chemical could meet the section 4(f) criteria when there may be a reasonable basis to conclude that it presents a risk from one of three effects--cancer, gene mutations or birth defects, and that the risk of this effect is significant and either serious or widespread. None of these terms--significant, serious or widespread--is precisely defined in TSCA.

The common technical use of these terms in the bio-medical sciences would suggest that "significant" would address both the probability that a risk of any magnitude could occur as well as the magnitude of the risk; and that "serious" and "widespread" would address the nature (i.e., major vs. minor) of any harm resulting and the size of the affected population, respectively.

For purposes of illustration, the following examples of usage are possible:

"Significant" -

> A particular animal cancer bio-assay indicates that chemical compound X is a carcinogen in at least two species tested and all sexes in these species. Compound X generally may present a risk of being a human carcinogen. To be "significant" it should further be established that--at human exposure levels--the risk is probable and would be high. A different chemical, compound Y, is positive in one species, one sex and at one high dose. It could, in theory, be a human carcinogen but it need not generally be considered to pose a "significant" risk to humans based solely on the one positive finding. Strong evidence for human risk should generally require that the carcinogenic effect be established as active in more than one species or at more than one dose.

> If for compound X above, it were found that the carcinogenic effect is due to activation of a metabolic pathway not found in humans, then the risk from compound X could be deemed not "significant" as it would not occur in humans.
>
> The carcinogenic effects of compound X could also be found to be secondary to physiological events (deposition of microcallculi, hormonal changes, necrosis, etc.) triggered by compound X at levels used in bio-assays but not at levels to which humans are exposed. Compound X would probably not pose a "significant" risk to humans. (See footnote 1)

"Serious" -

> The concept of "serious" harm would have more utility in the consideration of gene mutational events or birth defects than in the case of cancer since malignant neoplasms in general are serious. Section 4(f) also draws a distinction between benign and malignant growths by use of the term "cancer" rather than "tumors".

"Widespread" -

> A teratogen could produce a minor anomaly. If this occurred at one in one hundred thousand births, it need not be necessarily "serious" or "widespread". The same outcome at one in one hundred births, however, would certainly be "widespread".

The determination that a chemical meets the criteria of section 4(f) is, by statute, made by the Administrator of EPA.

When a chemical meets the criteria for section 4(f) priority status, the Agency must decide quickly whether to initiate action. The provision states that the Administrator must, within 180 days of the Administrator's receipt of the information

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(1) These considerations as to weight of evidence to establish human risk generally follow the recognized International Agency for Research on Cancer (IARC) criteria (IARC, Internal Technical Report No. 78/003) as to whether evidence is negative, limited, or sufficient for human carcinogenicity as well as the amplification of these criteria presented by Griesemer and Cueto (Scientific Publication No. 27, IARC, Lyon; p. 259-281 (1980)). The second paragraph draws from Weisburger and Williams (in Toxicology, Casarett and Doull, Eds., 2nd edition, MacMillan, N. Y. (1981) as well as from a more recent paper of Squire (Science, 214; 877-880 (1981)).

indicating the risk, initiate appropriate action under section 5, 6, or 7 of TSCA, or explain in the FEDERAL REGISTER why the risk is not unreasonable. As a purely technical matter, only rarely would a single study provide a reasonable basis to conclude that a chemical presented or would present a significant human risk. Risk is a function of toxicity and exposure. Therefore, exposure evaluations (which generally must rely on other studies than those raising toxicological concerns) are required in order to properly quantitate risk. The probability that risk would indeed occur can in general, likewise, only be assessed by review of all the available literature on a given chemical. Only when the diverse pieces of information which must go into a proper risk assessment are assembled into a reasoned evaluation can there generally be any scientific basis on which to draw reasonable conclusions as to the nature of human risk posed by a given chemical.

In certain instances the available data on a chemical may suggest that it poses a human risk but be insufficient to reasonably support a conclusion that the chemical presents a significant risk of serious or widespread harm [i.e., similar to a section 4(f) determination] and/or an unreasonable risk [a determination called for in other parts of TSCA]. The distinction between chemicals which may pose a human risk and those which pose either a significant and/or unreasonable risk [applicable to section 4(f) and/or section 5, 6, or 7, respectively] is important from a policy standpoint. This distinction and the TSCA data collection authorities allow the Agency to deal with chemicals on which the data are suggestive but inconclusive by use of sections 4(a), 5(e), and/or 8 so as to better develop a data base. This distinction also allows the Agency to place less priority on such substances as may be found to pose less than significant human risk even though the Agency may want to retain some oversight of activities involving such a substance.

## Applicability of TSCA Section 4(f):

The principle decision before the Administrator at present is whether or not the data available on formaldehyde meet the criteria set out in section 4(f) of TSCA. The technical and policy arguments that these criteria are not met are presented for each substance in this report in greater detail below. Legal conclusions as to section 4(f) are not within my realm of expertise. In this report I have tried to define the technical practicalities of section 4(f) and to address the relevant policy issues.

Generally, the approach to section 4(f) that is presented is that, until the Administrator has reviewed the available data and reached a conclusion as to the significance of risk, any designation of data as having triggered section 4(f) is scientifically arbitrary. This has tremendous practical and scientific underpinnings as, in general, no one study by itself will be sufficient to indicate "significant" risk and the required determination that "there may be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant risk . . . " should, therefore, require a synthesis of existing and newly developed knowledge. Only when this synthesis is accomplished can a reasoned conclusion, in general, be reached.

As a policy matter, it is recommended that risk situations which are "significant" in the context of priority setting via section 4(f) be clearly distinct from risk situations which are generally not of immediate regulatory interest. In terms of individual lifetime cancer risks, the various federal agencies do not tend to regulate risks of $1 \times 10^{-5}$ or lower and tend to be ambivalent about risks between $1 \times 10^{-4} - 1 \times 10^{-5}$. Certainly (as absolute risks) these risk levels could never be detected any normal way and would (using $1 \times 10^{-4}$ as an upper bound) represent increments of 0.03% or less above the estimated individual risk of persons in the U.S. population as a whole. (This risk is 1 in 3 or $3.3 \times 10^{-1}$ according to the most recent National Cancer Institute figures.) In OPTS the relative risk range of $1 \times 10^{-4}$ to $1 \times 10^{-6}$ or lower has been a low concern range in general. The use of a range is appropriate since these risks, even at the 95% upper confidence limit, are only relative estimates for specific chemicals. To use such risk estimates as absolutes is inappropriate. This point was recently emphasized by Dr. David Rall, Director of the National Toxicology Program, in testimony before Rep. Gore during the 1981 NTP appropriations hearings.

## FORMALDEHYDE:

### Summary

Technical and policy discussion of these points is to be found in the body of this report.

### Conclusions With Respect to Formaldehyde:

I concur with the recommendations of OTS staff that formaldehyde does not meet the criteria of section 4(f) for the following reasons:

(A) There is suggestive evidence that there may be human exposure situations--based on the integrated animal data base--which may not present carcinogenic risk which is of significance.

(B) There is a limited but suggestive epidemiological base which supports the notion that any human problems with formaldehyde carcinogenicity may be of low incidence or undetectable. It would not appear reasonable to say that a significant risk situation exists from these data.

(C) Assuming that risk--of some magnitude--does exist the calculated relative risks tend to fall into ranges which normally are of from low priority to no concern such as those discussed in the section immediately above on the applicability of TSCA section 4(f).

(D) One can, therefore (and as amplified below) conclude on the basis of available toxicological data, exposure information, and risk analysis techniques that: (a) formaldehyde is a carcinogen in the rat by the inhalation route; (b) its carcinogenic potential appears to vary significantly with species and route; (c) under certain exposure conditions it could present some carcinogenic risk to humans; and (d) given available data the risk estimates suggest that certain populations may experience a carcinogenic risk--albeit low--due to formaldehyde exposure. However, because of the nature of the toxicology data and the unreliability in the exposure data one cannot reasonably conclude, at this time, that formaldehyde poses a significant risk among the U.S. population.

Interpretation of Animal Studies with Respect to Human Risk -- Of a variety of bioassays (Table I) done since 1954 to assess the carcinogenic potential of formaldehyde only two have given clear positive results attributable to formaldehyde: a Chemical Industry Institute of Toxicology Study (CIIT) reported in preliminary form by Swenberg et al, Cancer Research, 40, 3398 (1980) and a study underway at the New York University Medical Center which is an extension of an earlier New York University study of 1979. Both of these have been inhalation studies in the rat. The CIIT study used three dose levels plus a control, the New York University study used a single high dose equivalent to the highest CIIT dose. Only nasal carcinomas were found in either study. Approximate mean lifetime incidences were 0% in control rats; 0% in rats at 2.1 ppm formaldehyde; 1.9% in rats at 5.6 ppm (not statistically significant); and 50% in rats at 14.1 ppm in the Swenberg study. The New York University study indicates (by letter of August 17, 1981 from Dr. Arthur Upton) an incidence of about 10% in rats at 14 ppm of formaldehyde.

Table I: Studies Considered in Evaluating the Carcinogenic Potential of Formaldehyde

| Species | Route | Dose | Length | % Incidence | Reference |
|---|---|---|---|---|---|
| Rat, ♀ & ♂, Fischer 344 | inhal. | 0, ppm<br>2.1 ppm<br>5.6 ppm<br>14.1 ppm | 24 mos. | (0%)<br>(0%)<br>(1.9%)<br>(50%) | CIIT study of Swenberg et al, nasal tumors only |
| Rat, ♂ Sprague-Dawley | inhal. | 14 ppm | lifetime (19 mos. completed) | (~10%) nasal tumors | On going NYU study reported by Upton letter of Aug. 17, 1981 |
| Rat, ♂, Sprague-Dawley | inhal. | 14 ppm+ 10 ppm HCl | lifetime (27 mos.) | (27%) nasal tumors | NYU study of Laskin et al |
| Mouse, ♂ + ♀, B6C3F1 | inhal. | 0 ppm<br>2.1 ppm<br>5.6 ppm<br>14.1 ppm | 24 mos. | - (0%)<br>- (0%)<br>- (0%)<br>(2%) | CIIT study of Swenberg et al, nasal tumors only |
| Hamster, ♂ Syrian | inhal. | 10 ppm<br>30 ppm | lifetime | - (0%)<br>- (0%) | Netteshein, NCI - DOE study, 1977 |
| Rat | s.c.[a] | formalin, 0.4%, 1 ml per animal weekly | 15 mos. | (40%) | Watanabe et al, Gann, 45, 451 (1954) sarcomas at injection site only. |
| Rat | s.c. | HMT,[b] 40%. 2 ml per animal per week | until tumor development | (40%) | Watanabe et al, gann, 46, 365 1955 sarcomas at injection site. |
| Rat, ♂ + ♀ BD | oral gavage | HMT, 0.4 g/day | 12 mos. | (0%) | Brendel, Drug Res., 14, 51 (1964) |
| Mice (CTM, SWR, and C3Hf) and Rat (Wistar) | drinking water | HMT, 2.5 g/Kg/d<br>" | 1 yr<br>2 yr | (0%)<br>(0%) | Della Porte et al, Food Cosmetic Tox., 6, 707 (1968)[c] |

Notes to Table:

a - sc = subcutaneous injection

b - HMT = hexamethylene tetramine

which decomposes in aqeous solution to give formaldehyde and ammonia with the stoichiometry:

$$1\ HMT \rightleftharpoons 4\ NH_3 + 6\ CH_2O$$

One gram of HMT is equivalent to 1.3 gram of free formaldehyde.

c - Della Porte et al, Tumori, 56, 325 (1970) also report a 3 generation study on Wistar rats with 2% HMT in drinking water which was negative for all three generations. This level of HMT is equivalent to about 2.5 g/Kg/d of ingested HMT which would be 3.3 g/Kg/d of formaldehyde.

The two studies used different strains of rat but are in general agreement. The CIIT study also exposed mice to formaldehyde gas but no statistically significant increase in tumors was observed. (See footnote 2.)

Other studies (some in other species and/or by other routes) have been generally negative save for a rat study of 1954 (expanded in 1955) using a subcutaneous injection route for 0.4% formalin or up to 40% hexamethylene tetramine (HMT, which gives rise to free formaldehyde, 1 gram HMT = 1.3 gram formaldehyde). In this study only sarcomas at the site of injection were found and these studies are not, therefore, generally accepted as being other than suggestive evidence of carcinogenecity. Significantly, the oral administration of hexamethylene tetramine to rats at up to 12.5 g/Kg/week was found to produce no tumors in three different investigations of up to two years duration (the same length as the CIIT inhalation study) conducted in 1964, 1968, and 1970. The oral route studies are somewhat limited by small sample sizes but, taking all three studies in aggregate, there is evidence which suggests a lack of a carcinogenic effect by this route. An important observation is that inhalation by hamsters at similar or higher exposure levels than used in the CIIT study has given a negative result. Formaldehyde appears, therefore, to exhibit considerable species specificity with the rat, the most sensitive of species so far tested.

Concern that formaldehyde gas may induce tumors in humans should be tempered by this observation that formaldehyde carcinogenicity appears to have a high degree of species specificity and a strong dependence on route of exposure. The rat, an obligatory nose breather, appears to have a particular nasal sensitivity to the deleterious effects of formaldehyde which may not be generally shared by other animals (man is not an obligate nose breather) or body sites. Based on the animal experimentation data, the most reasonable interpretation is that formaldehyde has carcinogenic potential, is probably locally acting, and is capable of both initiation and promotion.

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(2) The statistical significance of the CIIT results at 5.6 ppm in the rat (1.9% incidence observed) and 14 ppm in the mouse (2% incidence observed) was determined by CIIT as described in the CIIT document "Data Released to the International Agency for Research on Cancer (IARC) Working Group", dated October 19, 1981, which is appended as Appendix A.

The results of the CIIT bioassay are, however, sufficient to establish that formaldehyde is a potential animal carcinogen with mode and degree of exposure quite important to the toxic outcome. Based on the observed differences in response shown by rats, mice, and hamsters, different species have differing sensitivities. This may be a quantitative rather than a qualitative difference but the negative results of inhalation studies with Syrian hamsters at up to 30 ppm formaldehyde suggest that there may be qualitative differences in response among species as well. It can, however, be prudently expected that under appropriate conditions of exposure formaldehyde gas may pose a cancer risk to the respiratory tract of humans (i.e.: nasal and buccal cavities, trachea, bronchial trees, and lungs, see footnote 3). In the CIIT bioassay (see Appendix A), the development of nasal carcinomas was always preceded by hyperplasia, metaplasia and overt signs of cytotoxicity to the nasal mucosa (simply put, the animals developed open sores in their nasal tissues after which tumors appeared). In other cases, with other chemicals, where tumors appear to be secondary to cytotoxicity, no observable effect levels of exposure have been postulated (see, for example, Weisburger, J. H. and Williams, G. M. in Casarett and Doull's Toxicology, 2nd ed., MacMillan, NY (1981)). Since formaldehyde has genotoxic properties, any simple analysis is complicated but the findings of the CIIT research team which supported the bioassay have bearing on the interpretation of the results of the bioassay:

(1) At low exposure levels or short exposure times the hyperplastic and metaplastic effects of formaldehyde exposure were reversible. This suggests that a higher exposure level or longer exposure time may produce a qualitatively different outcome with respect to carcinogenesis than would result from low level or short term exposure.

(2) Normal endogenous tissue levels of formaldehyde produced by metabolism range from 3-12 Ng/g tissue (3-12 ppm). Much of this appears to be bound up as adducts to glutathione, tetrahydrofolate, and proteins. From 10%-40% of the total tissue formaldehyde appears to exist as free formaldehyde (0.3 Ng/g - 4.8 Ng/g). A sustained exposure of 3 ppm formaldehyde in air is needed to double the endogenous level of formaldehyde.

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(3) Other body sites are theoretically possible targets but, due to a variety of studies demonstrating rapid metabolic conversion of formaldehyde at or near the sites of uptake (Maloney, 6, *et al*; *Arch. Exp. Pharmacol.*, *250*; 419-436 (1965); McMartin, K.E., *Biochem. Pharmacol.*, *28*; 645-649 (1979)) it is expected that the respiratory tract will be the principal, possibly sole, target organ at risk. A high degree of site concordance between humans and animals has been suggested by Tomatis (L. Tomatis *et al*, *Cancer Research*, 38; 877 (1978)).

(3) There appears to be an absence of cytotoxic effects of formaldehyde at or below 1.0 ppm in air.

(4) Radio-isotope tracer measurements indicate that absorption of formaldehyde gas from inspired air is essentially complete within the nasal cavities and formaldehyde gas does not reach the trachea, bronchi or lungs of rats at the exposures used in the CIIT study.

(5) Formaldehyde is a mutagen. As such it is a potential genetoxic carcinogen. Aldehydes, as a chemical class, are also promoters of carcinogenesis (Slaga, T. J., Sivak, A.; and Boutwell, R. K.; Mechanisms of Tumor Promotion and Cocarcinogenesis, Raven Press, NY, 1978). Formaldehyde can, then, potentially both initiate and promote the carcinogenic process. A promoting and/or cocarcinogenic effect of formaldehyde is supported by other studies cited in Table I, in particular the various New York University studies. Promotion generally requires repeated, long term exposure to the promoter and is reversible [(Weisburger, J. H. and Williams, G. M.; "Chemical Carcinogenesis" in Holland, J. F. and Frei, E. (eds): Cancer Medicine, 2nd ed., Lea and Febiger, Philadelphia, 1980)], may involve damage to cellular components (Slaga et al (supra), 1978), and is a requisite, at some point, to the carcinogenic process. When taken together with the observations reported by CIIT on the reversibility of hyperplastic and metaplastic effects (vide (1) supra) and an apparent cytotoxicity threshold (vide (3) supra) the degree to which formaldehyde promotes its own carcinogenesis may lead to qualitative, as well as quantitative, differences in response within different regions of the dose-response curve.

An argument can be made that any initiating effects of formaldehyde would, nonetheless, produce a population of latent malignant cells. These cells could then produce malignancies in response to other promoters (endogenous or exogenous) as the animals grew older. In such a case the difference in response to formaldehyde exposure at different exposure levels would be only quantitative and not qualitative. This argument is a classical one (See Weisburger and Williams, 1981, supra) and has some merit as a general argument. It needs to be discussed, however, in the context of formaldehyde as it affects the nasal mucosa.

Clearly, in the absence of detoxifying mechanisms, the endogenous levels of formaldehyde should be potentially capable of initiating some cells. The observed absence of nasal carcinomas in rodents as spontaneous tumors (for example, Dr. A. Upton communicates by letter of August 17, 1981, that in 14 years with 1,920 rats he has not observed a single grossly visible nasal carcinoma) indicates one of four things: (a) no cells are in fact initiated by endogenous levels of formaldehyde or repair processes at low exposure are faster than processes leading to cell transformation; (b) there are not endogenous promoters available to allow expression of the transformed cells; (c) any cells initiated are lost before their malignant potential can be expressed or (d) the tumor incidence is so low as to be undetectable.

The first situation would de facto, define a practical threshold for genotoxicity. Formaldehyde is an endogenous metabolite and it is possible that mammalian cells may deal effectively with low levels of it.

The second situation could suggest that promotion by exogenous factors (formaldehyde could be one) was the controlling element in formaldehyde carcinogenesis. This would imply a lack of carcinogenic effects at exposures to exogenous factors which did not result in promotion. The observation, by CIIT, that tumor formation could be secondary to a formaldehyde induced cytotoxicity, hyperplasia, and metaplasia does suggest that the promoting effects of formaldehyde may be quite important. At low exposure levels the hyperplastic, metaphastic, and cytotoxic effects observed were reversible in the CIIT study.

The third situation is probably relevant to the question of formaldehyde carcinogenesis. Normally, the epithelia of the nasal mucosa loses matured cells which are then daily replaced by underlying stem cell layers. Thus, cells which might be initiated by formaldehyde could be lost from the epithelia before their malignant potential could be expressed. This possibility has not however, been addressed experimentally.

The fourth consideration may have some bearing but in a variety of studies (CIIT and those of Dr. Upton's colleagues at NYU) over 2,000 rats have been observed as a historical control. If nasal carcinoma occurs spontaneously in rats, its incidence would be very low. (See footnote 4)

The observed lack or low incidence of spontaneous nasal carcinoma in rats--given the endogenous levels of formaldehyde present--is probably explained by a combination of the above

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(4) One rat developing a tumor per 2,000 animals would be an incidence of $5 \times 10^{-4}$. This is not the same as the level of risk to rat or, possibly, human but suggests that individual risk from endogenous tissue levels of formaldehyde might be bounded by numbers of similar magnitude.

considerations. The net result is that there would appear to exist some lower bound to the observable carcinogenic effect of formaldehyde resulting from exposure to exogenous sources.

As such, the above considerations regarding endogenous levels of formaldehyde coupled with observations of CIIT of the reversibility of formaldehyde related effects at low exposure levels suggest that low level exposures (<1-2 ppm) probably would not present a significant risk of a carcinogenic outcome. The CIIT radio-isotope work also would suggest that carcinogenic risk from airborn formaldehyde could be restricted to the nasal and oral cavities. According to IARC documents there is nearly an 80% site concordance between humans and animals for those human carcinogens adequately testing in animal systems (L. Tomatis et al, Cancer Res. 38, 877 (1978)).

Considertion of Existing Epidemiology Data - A number of small scale retrospective epidemiology studies on groups occupationally exposed to formaldehyde have found no excess of cancers of any type, in particular nasal or oral, in these groups which can be attributed to formaldehyde exposure when corrected for smoking and drinking. The annual incidence of human nasal cancer is about one in one million (1 x 10$^{-6}$). While I recognize the limits of sensitivity inherent in epidemiology, such data are useful. In particular, for chemicals of long standing and well defined use, epidemiology could tell if a critical situation exists. If formaldehyde were a potent human risk, this should show up epidemiologically. There does not appear to be any relationship, based on the existing data base on humans, between exposure and cancer. Real human risk could be considered to be low on such a basis.

Human Exposure to Formaldehyde - Human exposure to formaldehyde is at levels generally much lower than those used in the rat inhalation studies. Typical values are ca. 0.005 - 0.3 ppm in ambient air in urban areas, 0.0004 - 0.005 ppm in rural locations, and 0.1 ppm in urea-formaldehyde (UF) foam insulated dwellings. It has not been possible to demonstrate a statistically significant difference in exposure levels in UF foam homes as opposed to non-UF homes. Occupational exposures can be higher but are generally less than 2 ppm formaldehyde. These occupational exposures are, also, for short periods and of an intermittent nature. Table II presents a distribution analysis of exposure levels.

### TABLE II: FREQUENCY DISTRIBUTION OF EXPOSURE ESTIMATES IN FORMALDEHYDE PRL-1 TECHNICAL DOCUMENT

These data are extracted from the integrated exposure assessment in the PRL-1. Only estimates given for populations of a known size are considered. High and low refer to the upper and lower bounds of estimated exposure ranges.

| INTERVAL (ppm) | Number of estimated exposed individuals | | | |
|---|---|---|---|---|
| | Low | Percentage of Total Individuals Exposed | High | Percentage of Total Individuals Exposed |
| 0 - 0.1[b] | $2.24 \times 10^8$ | 99.4[a] | $2.20 \times 10^8$ | 97.6[a] |
| 0 1 - 0.5 | $7.09 \times 10^4$ | 0.03 | $4.50 \times 10^4$ | 0.02 |
| 0.5 - 1.0 | $3.00 \times 10^4$ | 0.01 | - | - |
| 1.0 - 2.0 | $3.04 \times 10^4$ | 0.01 | $5.89 \times 10^4$ | 0.03 |
| 2.0 - 5.0 | $1.24 \times 10^6$[c] | 0.55 | $3.86 \times 10^6$[d] | 1.71 |
| 5.0 - | - | - | $1.26 \times 10^6$[e] | 0.56 |

[a] % of total individuals exposed

[b] includes U.S. population via ambient air

[c] 97% are college students who on an average are exposed to an estimated 8.3 ppm for very short periods and over a limited time. Humans cannot tolerate formaldehyde exposures above 5 ppm and so this group is probably exposed to far less than the PRL-1 average estimate.

[d] 57% are mobile home residents at an average 0.4 ppm; 40% are U.F. home residents at an average of 0.72 ppm

[e] 95% are the same college students as in footnote c.

Humans do not adapt to levels of airborne formaldehyde over 5 ppm and levels from 2 - 5 ppm are generally very unpleasant. The "high" side of the PRL-1 exposure ranges should, then, be viewed critically as this suggests a very sizeable group is exposed - on a regular basis - to levels of formaldehyde above 2 ppm. It must be noted that for the group footnoted as (d) in Table II, the "high" value derives from short transients in complaint homes and is non-representative. The appropriate averages are indicated in the footnote. The exposure group footnoted as (e) in Table II, similarly is constituted by using a single excursion, transient as an upper bound on the range of exposure. The footnote (c) explains that PRL-1 assigned these college biology students an average exposure of 8.3 ppm several hours a week. Clearly, this number is not to be relied on since humans cannot breathe in such an environment. The column listed under "low" is to be taken as more representative (with the possible exception of the college biology students). Table II suggests, then, that nearly all prolonged human exposures are at levels well below 2 ppm.

Given that quantitative and possibly qualitative results of exposure to formaldehyde appear to depend highly on exposure level, species, and route; that rats seem to be particularly sensitive to formaldehyde; and that long human experience does not seem to indicate any pressing concerns; I must concur with OTS' staff recommendations in this matter - that formaldehyde ought not be considered subject to TSCA section 4(f) at this time.

Deficiencies in the Original OTS PRL-1 Document:

The original review of formaldehyde (PRL-1) was deficient in a number of areas -

(1) Exposure Estimates: This was the major deficiency in the original document. In many situations the exposures given were not obtained by analytical methods similar to that used to monitor formaldehyde levels in the CIIT study. No attempt was made to address the comparability of methods so it is not clear that 1 ppm by any given method equates to 1 ppm exposure under the CIIT protocol. This has the effect of making any subsequent risk analysis (which must be exposure based) an "apples and oranges" comparison. Table III points out the various methodologies cited in studies covered by the PRL-1 document.

TABLE III: Number of Exposure Estimates by Type of Analytical or Collection Method in Formaldehyde PRL-1

| METHOD | NUMBER OF ESTIMATES | BASED ON METHOD[a] |
|---|---|---|
| | | as % of all studies |
| Acetylacetone | 1 | 1.1% |
| Bisulfite impingers | 18 | 20.7% |
| Chromotropic acid | 17 | 19.5% |
| Chemiluminescence | 3 | 3.4% |
| Colorimetry | 7 | 8.0% |
| Charcoal tubes | 9 | 10.3% |
| Solid sorbents | 1 | 1.1% |
| Draeger Tubes | 3 | 3.4% |
| FT Spectroscopy | 2 | 2.3% |
| Gas Chromatography | 1 | 1.1% |
| Ion Chromatography | 7 | 8.0% |
| MBTH Method | 1 | 1.1% |
| Spectrophotometry | 3 | 3.4% |
| Not Known | 14 | 16.1% |

[a] Number of studies in data base which cite a particular method. Some studies cite more that one method.

The PRL-1 review also used the highest values of formaldehyde found in any given monitoring study as its exposure levels for risk analysis. This is not well advised since these high levels are in most cases transients or single excursion values (i.e.: not continuous) and do not, therefore, represent the risk picture adequately. The tendency of the PRL-1 to use exposure levels greater than 2 ppm when calculating exposure to some populations is flawed as well since humans do not well tolerate exposures to formaldehyde which are higher than around 2 ppm. Even though some adaptation can occur, this is unknown above 5 ppm yet PRL-1 uses exposure levels above 5 ppm as prolonged exposures.

The poor quality of the exposure estimates is repeatedly acknowledged in the PRL-1 and forms the basis for the recommendations contained in the earlier draft Federal Register notice and action memorandum (see below). As such, any risk estimates given in the PRL-1 must be viewed very skeptically. It is not clear that such estimates would be a reasonable basis to do other than conclude that one needed better exposure data. This, in effect, is what OTS staff originally concluded and is in the earlier Federal Register notice draft of which NRDC has a copy.

(2) Evidence for Carcinogenecity: The PRL-1 concludes that formaldehyde is an animal carcinogen. It downplays a number of negative bioassays which suggest that its effects may depend highly on species, route and site. No attempt was made, also, to address the question of mechanism of action or other physiological/biochemical questions relevant to the extrapolation from rat to human even though such information was available from CIIT.

The discussion of human epidemiology emphasized studies which showed marginal differences in total cancer rates (i.e., the treatment of one study in which one cohort had a slight increase in total cancer tate relative to historical controls but a second cohort showed no such effect. Much was made of the "positive" cohort but the negative cohort was downplayed). No trend was seen toward increases in any specific cancer (as is common for human chemical carcinogens) in any study. The human data do not show signs (such as correlation to a specific tumor) usually seen for a human carcinogen and do not, as is discussed above, generally suggest any specific effect of formaldehyde.

Risk Assessment:

The PRL-1 document contained a risk assessment performed by use of the Crump multistage model and based on the high exposure estimates presented in the PRL-1 document. OTS staff has also calculated a risk analysis based on median (more representative) exposure values. Relative risks are calculated and expressed as 95% upper confidence limits on lifetime risks.

Table IV presents a population distribution of relative individual risks as calculated by OTS staff in PRL-1 using representative (median or average) exposure estimates. Risk is divided into order of magnitude ranges and the size of the affected population falling into each range is given. As can be seen nearly all individual risks fall into the range $1 \times 10^{-6} - 1 \times 10^{-4}$. This places them into a range in which priority action is often not considered. A similar situation exists for populations of unspecified size (Table V). Again, if the human risk were real, the magnitudes of individual risks do not seem to compel a "fast track" approach. This seems to have been recognized in the draft FR notice prepared in 1981 by OTS under Dr. Muir. That notice proposed to engage in a two year effort to collect exposure data so as to refine the risk calculations. This stemmed from the poor quality of the exposure analysis in PRL-1 and the low relative magnitude of the estimated individual risks.

The risk calculation used by OTS included the 5.6 ppm exposure level as a non-zero incidence data point. CIIT has since determined this point to be statistically no different than the 0 ppm and 2.1 ppm exposure results (see Appendix A). If this 5.6 ppm exposure were treated as a zero response point, the risk estimates of Tables IV and V would shift, in distribution, to yet lower values.

The risk estimates in PRL-1, also, do not take into account that tumor formation in rats appears to require a long term, high level exposure and that the human exposures are likely to be relatively short. Workers might see 1 ppm or less intermittently over a 40 year work career assuming no change in occupation (see footnote 5). College students in biology

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(5) The OSHA standard for formaldehyde is 3 ppm but OSHA documents indicate that workplace exposures are generally less than 1.5 ppm. OPTS staff agree that this is an appropriate and representative number as a general upper bound on workplace exposures.

TABLE IV: DISTRIBUTION OF RELATIVE INDIVIDUAL LIFETIME RISKS AS DERIVED FROM PRL-1 FOR FORMALDEHYDE

| Range of Risk | Population Size[a] | % of Total | |
|---|---|---|---|
| | | A | B |
| $10^{-6} - 10^{-4}$ (0.003)[b] | $2.14 \times 10^{8}$ | 99.9 | 95.0 |
| $10^{-4} - 10^{-3}$ (0.15) | $1.52 \times 10^{5}$ | 0.071 | 4.1 |
| $10^{-3} - 10^{-2}$ (1.5) | $3.13 \times 10^{4}$ | 0.015 | 0.9 |
| $10^{-2}$ (3) | 0 | - | - |

A: Total of all identified populations

B: Excluding ambient air and water exposures

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[a] This table applies only to exposed populations for which a size was estimated in PRL-1

[b] NCI data indicate that individuals of the U.S. population have an average individual lifetime risk of contracting cancer of $3.3 \times 10^{-1}$, the number in parenthesis is the % increment above this average represented by a risk in the center of each indicated range save for the last range in which case the % increment is that due to the boundary risk.

TABLE V: DISTRIBUTION OF GROUPS WITH UNSPECIFIED POPULATION SIZE BY RELATIVE RISK INTERVALS

Both maximum likelihood and 95% upper confidence estimates of relative individual lifetime risk are shown. For comparison, according to recent National Cancer Institute figures the absolute risk of contracting cancer over a lifetime is approximately 1/3 or $3.3 \times 10^{-1}$. For each risk interval the percentage increase in lifetime risk (assuming the risk estimates are absolutes which they are not) is presented.

| Interval | | Number of size | Undetermined groups |
|---|---|---|---|
| range | % incremental[a] | MLE[b]<br>Maximum likelihood estimate | ULOC[c]<br>Upper Limit of Confidence |
| $<10^{-5}$ | 0.003% | 6 | 0 |
| $10^{-5} - 10^{-4}$ | 0.03% | 3 | 7 |
| $10^{-4} - 10^{-3}$ | 0.3% | 2 | 3 |
| $10^{-3} - 10^{-2}$ | 3% | 0 | 1[d] |

[a] % increment above NCI determined lifetime risk of $3.3 \times 10^{-1}$

[b] Maximum likelihood estimate

[c] Upper limit of 95% confidence

[d] Represents one group with a 20 fold range in estimated exposures.

labs are, similarly, a large group (1.2 million individuals) which the PRL-1 assumes are exposed over 70 years. In fact, exposure of nearly all of these students would be generally on the order of one year or less.

Another factor not considered in the PRL-1 risk estimates is that the animal evidence would suggest that inhalation of formaldehyde by humans should produce tumors (if any are seen) primarily of the oral, pharyngeal and nasal mucosa (see footnote 3). These are well defined sites for which the limited epidemiological evidence does not suggest an association with formaldehyde exposure under what are poorly documented but probably representative conditions.

In summary, the PRL-1 does serve to identify some possible areas of concern. From a technical standpoint it would appear to be premature to "fast-track" any regulatory actions since we have estimates only on the upper bound of any risks and these do not, when reasonable assumptions are made, appear to be significant. The draft FR notice (discussed below) which was prepared by OTS on the basis of PRL-1 review acknowledged as much by specifying no regulatory actions per se. The proposed response was, rather, to conduct monitoring surveys of the actual exposure conditions so as to better quantitate the risk. This de facto recognizes that the PRL-1 numbers were highly unreliable and that a proper risk assessment had yet to be done. PRL-1 does not seem to sustain a reasonable conclusion that formaldehyde presents a significant risk of cancer to humans.

Deficiencies in the draft Federal Register notice on formaldehyde:

In 1981 OTS drafted a proposed Federal Register notice on formaldehyde for the signature of the Administrator.

This notice presented a logical sequence and I have analyzed the rationale employed as follows:

(A) Formaldehyde is an animal carcinogen;

therefore,

(B) it is a potential human carcinogen.

(C) Formaldehyde is a high volume chemical;

therefore,

(D) it presents wide spread exposure potential.

(E) Some individual exposures are estimated to be high;

therefore,

(F) some exposures are serious.

Given (B), (D) and (F), then

(G) Formaldehyde is a potential human carcinogen that presents serious or widespread exposures;

therefore,

(H) formaldehyde meets the section 4(f) criteria for "significant" risk of "serious" or "widespread" harm.

There are a number of flaws in this line of reasoning. Some are explicitly acknowledged in the draft FR notice but others are more subtle and need to be addressed first:

(1) The meaning of the term "significant" in the draft FR notice is not consistent with the common technical meaning as discussed above. No case is made for other than formaldehyde being a potential or possible human carcinogen. The degree to which this may or may not be an actuality (i.e., the significance of this risk in terms of probability of existence and magnitude if it exists--as discussed under Technical Issues above) is not addressed. Therefore the draft FR notice uses the words "significant" and "potential" synonymously.

(2) The assumption that a high production volume equates with a high or "widespread" exposure potential is very weak. In general, the degree of correlation between production volume and exposure will depend on uses and handling methods. A blanket assumption, as used in the FR draft notice, is not justifiable in the absence of supporting evidence.

(3) The conclusion that some individual exposures are "serious" is premised on faulty assumptions as to exposure levels as previously discussed.

The plain language of the statute calls for initiation of regulatory action under sections 5, 6 or 7 as the response to be made under section 4(f). The proposed gathering of exposure data--the response given by the FR draft--appears to be an acknowledgement that the significance of any risk from formaldehyde has not been reasonably evaluated since, as a result of gathering this exposure data, it is further proposed to evaluate risk to see if further action is appropriate. The premises and conclusions in the FR draft appear to be faulty.

DEHP:

No detailed analysis is presented of the DEHP situation since work culminating in the PRL-1 and draft Federal Register documents was based on incorrect exposure assumptions. The policy analysis given in the section on formaldehyde applies to the DEHP case.

For purposes of discussion and comparison, the risk estimates in the PRL-1 document are given and then discussed briefly:

Table: PRL-1 Risk Estimates

| Group | 70 yr Individaul Risks | Potential Cases[a] Over 70 years |
|---|---|---|
| hemodialysis patients (45,000) | $1 \times 10^{-3}$ | 45 |
| hemophiliacs (19,000) | $1 \times 10^{-4}$ | 1.9 |
| U.S. population via food (250 million) | $7.5 \times 10^{-7}$ | 188 |
| U.S. population via drinking water (250 million) | $6 \times 10^{-7}$ | 150 |
| [b]Occupational (as in PRL-1 originally) | | |
| Manufacturing (335) | $1 \times 10^{-4}$ | 0.03 |
| Processing (40,000) | $1 \times 10^{-4}$ | 4 |
| [b]Occupational (as revised by OTS) | | |
| Manufacturing (335) | $1 \times 10^{-5}$ | 0.004 |
| Processing (40,000) | $1 \times 10^{-6}$ | 0.04 |

a Assumes 95% upper confidence limit is an absolute risk, it is in fact relative and an upper bound on any relative risk present.

b Revised on the basis of exposure data presented at the 1980 pthalates conference.

It must be pointed out that the first two groups in the Table are not affected by TSCA since their exposure is a result of contact with medical devices under the purview of FDA. These are also groups which are at high risk from their diseases and the benefits of these medical devices should probably far outweigh the risks indicated. In any case, they cannot be factored into any analysis of TSCA applicability.

Estimates for the dietary risks to the U.S. population as a whole fall below the range in which regulatory agencies do not take any actions. The exposures were estimated as described in PRL-1 and are of good quality, in my opinion.

The drinking water estimate is the average number contained in PRL-1. I believe it to be representative and, again, the risks are below the range in which we would normally not act.

The original Federal Register document was driven largely by the occupational risks given in the table. The risks begin to push up into the range in which we would normally consider some action (regulatory or non-regulatory) but are, nonetheless, lower than what might push a priority designation. As a result of the 1980 phthalates conference, OTS staff realized that the exposure estimates which had been used to generate these risks were completely incorrect. In essence they postulated a DEHP concentration (as vapor in air) higher than the vapor pressure of DEHP could generate.

The exposures and associated relative risks were recalculated and are given in the PRL-1 Risk Estimates Table as revised occupational risks. With the revision of the occupational exposure numbers reason to take any action with respect to DEHP disappeared.

There has not, since the detection of the errors in occupational exposures, been any reasonable basis upon which DEHP could be considered to pose significant risk to humans - given current use patterns - and I concur with OTS staff that DEHP cannot be recommended to you as a candidate for section 4(f) designation.

As a final comment on DEHP, there are enough anomalies in the result of the NCI bioassay that I remain unpersuaded that DEHP should be considered a human carcinogen.

## Appendix A

# DATA RELEASED TO
# THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)
# WORKING GROUP

OCTOBER 19, 1981

Chemical Industry Institute of Toxicology (CIIT)
P. O. Box 12137
Research Triangle Park, NC 27709

### 3.1 Carcinogenicity studies in animals

#### (b) Inhalation and/or intratracheal administration

Mouse

Groups of 120 male and 120 female B6C3F1 mice, 6 weeks of age, were exposed to 0, 2.0, 5.6 or 14.3 ppm (0, 2.46, 6.89, 17.59 $\text{ng/m}^3$) formaldehyde (> 97.5% pure) vapor by whole-body exposure for six hours per day on 5 days per week, for up to 24 months. A 90 day sub-chronic study utilized to set the exposure levels demonstrated necrosis of the nasal mucosa and death after 2 weeks exposure to 40 ppm. The number of mice involved in scheduled sacrifices and unscheduled deaths is shown in Table 1. All tissues from control and high exposure mice and multiple sections of nasal cavity and all gross lesions from all low and mid-exposure mice, as well as all tissues from unscheduled deaths in these groups were evaluated histopathologically.

Concentration related effects of formaldehyde exposure on mouse survival were not apparent, however, substantial mortality did occur in all groups of male mice. This was primarily attributed to fighting and ascending urinary tract infections. Exposure of mice to 14.3 ppm formaldehyde vapor resulted in diminished body weight. Using life-table analysis, a number of lesions in the nasal cavity were significantly increased ($p < 0.0167$). These lesions included epithelial dysplasia at 5.6 and 14.3 ppm in males and females; squamous metaplasia at 5.6 and 14.3 ppm in males and 14.3 ppm in females; purulent or seropurulent rhinitis at 14.3 ppm in males and females; and olfactory epithelial atrophy in 14.3 ppm female mice. Squamous cell carcinomas occurred in the nasal cavities of 2 male mice, but no females. Neither life-table analysis nor the Fischer exact test revealed statistical significance (Kerns et al., 1982a,b).

Table 1. Number of formaldehyde-exposed mice involved in scheduled sacrifices and unscheduled deaths

| Exposure (ppm) | Sex | Scheduled Sacrifice |  |  |  |  | Unscheduled Deaths |  | Total |
|---|---|---|---|---|---|---|---|---|---|
|  |  | 6 mo | 12 mo | 18 mo | 24 mo | 27 mo | 0-24 mo | 24-27 mo |  |
| 0 | Male | 10 | 10 | 0 | 21 | 0 | 78 | 0 | 120 |
| 0 | Female | 10 | 10 | 20 | 31 | 16 | 30 | 4 | 121 |
| 2.0 | Male | 10 | 10 | 1 | 22 | 0 | 77 | 0 | 120 |
| 2.0 | Female | 10 | 10 | 20 | 26 | 12 | 34 | 8 | 120 |
| 5.6 | Male | 10 | 10 | 0 | 19 | 0 | 81 | 0 | 120 |
| 5.6 | Female | 10 | 10 | 20 | 41 | 11 | 19 | 9 | 120 |
| 14.3 | Male | 10 | 10 | 0 | 17 | 0 | 82 | 0 | 119 |
| 14.3 | Female | 10 | 10 | 19 | 28 | 9 | 34 | 11 | 121 |

Rats

Groups of 120 male and 120 female Fischer 344 rats, 7 weeks of age were exposed to 0, 2.0, 5.6 or 14.3 ppm (0, 2.46, 6.89 or 17.59 ng/m$^3$) formaldehyde (> 97.5% purity) vapor by whole-body exposure for six hours per day on 5 days per week, for up to 24 months. A 90 day sub-chronic study utilized to set the exposure levels demonstrated weight loss and mucosal erosions of the nasal turbinate in rats exposed to 12.7 ppm and mortality and ulceration of the nasal turbinates and trachea after 2 weeks of exposure to 40 ppm. The number of rats involved in scheduled sacrifices and unscheduled deaths is shown in Table 2. All tissues from control and high exposure rats and multiple sections of nasal cavity and all gross lesions from [illegible] low and mid-exposure rats, as well as all tissues from unscheduled deaths in these groups, were evaluated histopathologically.

Rat survival was adversely affected by exposure to 14.3 ppm. A summary of neoplastic lesions in the nasal cavity is shown in Table 3. Life-table analysis of these data revealed significant increases ($p < 0.0167$) in squamous cell carcinomas in both male and female rats exposed to 14.3 ppm formaldehyde vapor. Significant increases in other neoplasms were not detected in formaldehyde exposed rats. A variety of other lesions were significantly increased in formaldehyde exposed rats. These included epithelial dysplasia at 2, 5.6 and 14.3 ppm in males and females; squamous metaplasia at 2, 5.6, and 14.3 ppm in males and females; goblet cell hyperplasia at 2, 5.6, and 14.3 ppm in males and at 2 ppm and 14.3 ppm in females; hyperkeratosis at 14.3 ppm in males and females; purulent or seropurulent rhinitis at 2, 5.6, and 14.3 ppm in males and at 5.6 ppm and 14.3 ppm in females; squamous atypia at 14.3 ppm in males and females; olfactory epithelial atrophy at 14.3 ppm in males and females; respiratory epithelial hyperplasia at 14.3 ppm in males; goblet cell metaplasia of the olfactory epithelium at 14.3 ppm in males and females; and squamous epithelial hyperplasia at 14.3 ppm in males. The incidence of tracheal epithelial dysplasia and metaplasia was different from control animals at 14.3 ppm in both males and females. The incidence of squamous metaplasia in the nasal cavity in rats from the 2.0 and 5.6 ppm exposure groups regressed during the three month postexposure period (Swenberg et al., 1980; Kerns et al., 1982a,b).

Table 2. Number of formaldehyde-exposed rats involved in scheduled sacrifices and unscheduled deaths

| Exposure | Sex | Scheduled Sacrifice | | | | | | Unscheduled Deaths | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| (ppm) | | 6 mo | 12 mo | 18 mo | 24 mo | 27 mo | 30 mo | 0-24 mo | 24-30 mo | |
| 0 | Male | 10 | 10 | 20 | 54 | 10 | 6 | 6 | 4 | 120 |
| 0 | Female | 10 | 10 | 20 | 47 | 9 | 4 | 13 | 7 | 120 |
| 2.0 | Male | 10 | 10 | 20 | 50 | 10 | 4 | 10 | 6 | 120 |
| 2.0 | Female | 10 | 10 | 20 | 44 | 10 | 1 | 16 | 9 | 120 |
| 5.6 | Male | 10 | 10 | 20 | 41 | 10 | 3 | 19 | 7 | 120 |
| 5.6 | Female | 10 | 10 | 20 | 41 | 9 | 5 | 19 | 6 | 120 |
| 14.3 | Male | 10 | 10 | 20 | 13 | 5 | 0 | 57 | 4 | 119 |
| 14.3 | Female | 10 | 10 | 19 | 14 | 0 | 0 | 57 | 0 | 120 |

Table 3. Summary of neoplastic lesions in the nasal cavity of Fischer-344 rats exposed to formaldehyde vapor.

| Exposure group (ppm) | 0 | | 2.0 | | 5.6 | | 14.3 | |
|---|---|---|---|---|---|---|---|---|
| Sex | M | F | M | F | M | F | M | F |
| No. of nasal cavities examined | 118 | 114 | 118 | 118 | 119 | 116 | 117 | 115 |
| Squamous cell carcinoma | 0 | 0 | 0 | 0 | 1 | 1 | 51[a] | 52[a] |
| Nasal carcinoma | 0 | 0 | 0 | 0 | 0 | 0 | 1[b] | 1 |
| Undifferentiated carcinoma or sarcoma | 0 | 0 | 0 | 0 | 0 | 0 | 2[b] | 0 |
| Carcinosarcoma | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Osteochondroma | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Polyploid adenoma | 1 | 0 | 4 | 4 | 6 | 0 | 4 | 1 |

[a] Significantly increased over 0, 2.0, and 5.6 ppm (adjusted Cox-Tarone $p < 0.0167$).

[b] One animal also had a squamous cell carcinoma

## 3.2 Other relevant biological data

### (a) Experimental systems

Toxic effects

Acute cell degeneration, necrosis and inflammation, were evident in the nasal cavities of rats exposed to 15 ppm formaldehyde vapor for 1 to 9 days (6 hrs/day) (Swenberg et al., 1982). Initial lesions were most severe on the tips of the maxillo and nasoturbinates. Acute degeneration and sloughing of the respiratory epithelium, with edema and congestion were evident at the end of 1 day's exposure. This was followed by ulceration, necrosis and an influx of inflammatory exudate at days 3-9. Early squamous metaplasia was detected over the naso- and maxilloturbinates, median septum and lateral wall after as little as 5 days of formaldehyde exposure. Examination of turbinates from rats exposed 5 days and allowed to recover for 48 hours demonstrated considerable regeneration. Areas which were frequently ulcerated, such as the lateral wall, had single thin strap cells covering areas normally occupied by 5 or more cuboidal epithelial cells. In contrast to these changes in the respiratory epithelium, mild serous rhinitis was the principal lesion in regions of olfactory epithelium. Mild degenerative and inflammatory changes were also evident in the nasopharynx.

The mouse was similar, but less severe than the rat in its acute response to formaldehyde toxicity. Five days exposure to 15 ppm formaldehyde vapor caused degeneration, focal necrosis and inflammation to the naso- and maxilloturbinates and to the lateral wall, but minimum toxicity to areas lined by squamous and olfactory epithelium. By comparing these acute data with results from the 6 month interim sacrifice (Kerns et al., 1982a,b), it is clearly evident that adaptive changes have occurred. The extent and severity of formaldehyde-induced toxicity diminishes with time. This may be due to changes in respiratory physiology, as well as alterations at the cellular level, ie. squamous metaplasia, epithelial hyperplasia and increased detoxification pathways.

## Effects of formaldehyde exposure on cell turnover

A prominent response to cell loss associated with toxicity is compensatory cell replication. Surviving cells undergo division in order to replace dead cells. Exposure of rats to formaldehyde vapor for 3 days (6 hrs/day) resulted in increased cell replication in rats at 6 and 15 ppm and mice at 15 ppm. No increase was detected in rats exposed to 0.5 or 2 ppm or mice exposed to 0.5, 2 or 6 ppm (Swenberg et al., 1982).

## Studies on the distribution and metabolism of formaldehyde in the nasal cavity

Biochemical investigations on the absorption and distribution of $^{14}C$-formaldehyde have demonstrated that $H_2CO$ is primarily absorbed in the upper respiratory system (Heck et al., 1982). Following a 6-hr exposure, the amount of $^{14}CH_2O$ absorbed appears to be directly proportional to the airborne concentration. This result is consistent with the high water solubility of $CH_2O$. It is important as well that the amount of $^{14}CH_2O$ absorbed did not appear to vary following pre-exposure. Hence, these findings, which are based on single exposures, may also be relevant to the chronic toxicity of $CH_2O$.

The extensive distribution of radioactivity to other tissues indicates that absorbed $^{14}CH_2O$ or its metabolites are rapidly removed by the mucosal blood supply. It is, however, unlikely that this radioactivity is primarily due to $^{14}CH_2O$. Rapid metabolism in the blood and tissues would probably reduce the concentration of free $CH_2O$ to extremely low levels.

The disposition and pharmacokinetic studies indicate that inhaled $CH_2O$ is extensively metabolized. It is likely that folic acid plays an important, perhaps a pre-eminent, role in this incorporation. However, the possibility that $^{14}CH_2O$ may form covalent adducts in vivo, or that $^{14}CO_2$ may itself be incorporated via carboxylation reactions cannot be excluded. The metabolism of inhaled $^{14}CH_2O$ appears to be similar to that which occurs following other routes of administration.

In order to localize this absorption within the nasal cavity, naive or pretreated rats and mice were exposed to 15 ppm $^{14}$C-formaldehyde for 6 hours and prepared for whole-body autoradiography. Formaldehyde-associated $^{14}C$ was heavily deposited in the anterior nasal cavity of rats and mice. The amount of radioactivity correlated well with the distribution of lesions in similarly exposed animals. That is, activity was greatest in regions of respiratory epithelium over the maxillo- and nasoturbinates and the lateral wall. An exception was noted for the ventral portion of the nasal cavity lined with squamous epithelium. Radioactivity was heavily deposited in this area, however, minimal toxicity occurred. This is most likely accounted for by the relative insensitivity of squamous epithelium to formaldehyde intoxication and supports the concept that induction of squamous metaplasia is a host defense mechanism to formaldehyde toxicity. A portion of the radioactivity located in the ventral squamous regions may be the result of muco-ciliary flow and gravity, rather than direct exposure to formaldehyde vapor. As such, the radioactivity may represent covalently bound material rather than reactive formaldehyde. The extent of formaldehyde-associated radioactivity deposited in regions of olfactory mucosa of posterior sections of the nasal cavity was much less, with radioactivity primarily confined to the nasopharynx. No differences were apparent in formaldehyde distribution between naive rats and mice. When animals that had been exposed to 15 ppm of non-radioactive formaldehyde for 9 days prior to exposure to $^{14}C$-formaldehyde were compared to the naive rats and mice, the pretreated mice had less radioactivity (Swenberg et al., 1982).

This decrease in radioactivity is associated with a decrease in minute volume in mice exposed to formaldehyde (Barrow et al., 1982). If the minute volumes for rats and mice exposed to 15 ppm formaldehyde are used to calculate the amount of formaldehyde inspired, and this amount is normalized to the surface area of the nasal cavity (Gross et al., 1982), the "dose" of formaldehyde available for absorption is 0.154 and 0.075 μg/min/cm$^2$ in rats and mice, respectively (Barrow et al., 1982; Swenberg et al., 1982). Thus, the mouse nasal mucosa is exposed to half the amount of formaldehyde than the rat nasal mucosa is. This dose correlates well with tumor data, where the incidence of nasal carcinoma is similar in rats exposed to 5.6 ppm and mice exposed to 14.3 ppm of formaldehyde vapor (Kerns et al., 1982b).

## Mutagenicity and other short-term tests

The effects of formaldehyde were evaluated in the C3H/10T½ Cl 8 cell transformation system. Treatment of cells with 0.1 - 2.5 μg/ml of formaldehyde alone did not result in significant rates of transformation. If formaldehyde treatment was followed by continuous treatment with 0.1 μg/ml of the tumor promoter 12-O-tetradecanoyl phorbol-13-acetate (TPA), transformed foci were produced. Methanol and formic acid lacked significant transforming activity under either treatment regimen. The results suggest that formaldehyde is an initiating agent for C3H/10T½ Cl 8 transformation (Ragan and Boreiko, 1981; Boreiko and Ragan, 1982; Boreiko et al., 1981).

e has been shown to cause DNA-protein crosslinks in mouse L1210
l., 1981; Ross and Shipley, 1980) and V79 cells (Swenberg et al.,
protein crosslinks were repaired within 24 hours in both cell

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# APPENDIX 2

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DU PONT
ESTABLISHED 1802

E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
WILMINGTON, DELAWARE 19898

EMPLOYEE RELATIONS DEPARTMENT
MEDICAL DIVISION

May 18, 1982

## EPIDEMIOLOGIC STUDY OF CANCER DEATHS IN DU PONT WORKERS WITH POTENTIAL EXPOSURE TO FORMALDEHYDE

Attached is an epidemiologic study of cancer mortality among Du Pont formaldehyde workers. The study, by W. E. Fayerweather and S. Pell of Du Pont's Epidemiology Section, was initiated in 1980 in response to preliminary results from CIIT's chronic toxicology study of rats exposed by inhalation to formaldehyde.

The objective of the study was to determine whether occupational exposure to formaldehyde increases the Du Pont employee's risk of developing cancer. Special interest centered around cancers of the lung and upper respiratory tract, particularly the nasal cavities.

A case-control study of cancer mortality among Du Pont employees who had worked with formaldehyde was completed. Cancer deaths from 1957 through 1979 were studied at eight formaldehyde manufacturing or using plants. There were a total of 481 cancer deaths at these sites, 142 of which were among employees who had worked with formaldehyde.

The data were analyzed by tumor site, latent period, duration of exposure, exposure level and frequency, cumulative exposure index, age and year of death, and age and year of first exposure. Analyses of lung cancer deaths were adjusted for subjects' cigarette smoking habits.

In none of these analyses was the formaldehyde workers' relative risk of cancer significantly greater than 1.0 ($p > 0.05$). Of particular significance was that there were no nasal cancer deaths and no lung cancer excesses among employees who had worked with formaldehyde. These results were strengthened considerably by our ability to factor employees' smoking habits into the analyses.

Slight but statistically nonsignificant elevations in relative risks were observed for prostatic and bladder cancers. However, these elevations showed no indications of being causally related to potential formaldehyde exposure and appeared to be due to chance.

In short, a thorough analysis of the data suggested that cancer mortality rates in the Company's employees who had worked with formaldehyde were no higher than the rates among nonexposed coworkers. These results support the conclusion that airborne levels of 1 ppm time-weighted average and a 2 ppm ceiling provide adequate employee protection.

Should you have any questions concerning the study, please contact me at 302 - 774-9513.

Sincerely,

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# CASE-CONTROL STUDY OF CANCER DEATHS IN DU PONT WORKERS WITH POTENTIAL EXPOSURE TO FORMALDEHYDE

William E. Fayerweather
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May 17, 1982

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## ACKNOWLEDGEMENTS

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## ABSTRACT

The objective of this study was to determine whether occupational exposure to formaldehyde increases Du Pont workers' risk of developing cancer. Special interest centered around cancers of the lung and upper respiratory tract, particularly the nasal cavities.

A case-control study of cancer mortality among workers exposed to formaldehyde was completed. Cancer deaths from 1957 through 1979 were studied at eight formaldehyde manufacturing or using plants. These plants included Parlin (F&F), Belle (BIOCHEM), Parlin (PHOTO), Toledo (C&P), Toledo (F&F), Rochester (PHOTO), Perth Amboy (ELECTROCHEM), and Washington Works (PPD). There were 481 cancer deaths at these sites, 142 of which were among workers with potential exposure to formaldehyde.

The data were analyzed by tumor site, latent period, duration of exposure, exposure level and frequency, cumulative exposure index, age and year of death, and age and year of first exposure. Analyses of lung cancer deaths were adjusted for subjects' cigarette smoking habits.

In none of these analyses was the formaldehyde workers' relative risk of cancer significantly greater than 1.0 ($p > 0.05$). Of particular significance was that there were no nasal cancer deaths and no lung cancer excesses among workers exposed to formaldehyde. These results were strengthened considerably by the ability to factor workers' smoking habits into the analyses.

Slight, but statistically nonsignificant elevations in relative risks were observed for prostatic and bladder cancers. However, these elevations showed no indications of being causally related to formaldehyde and appeared to be due to chance.

In short, a thorough analysis of the data suggested that cancer mortality rates in the Company's formaldehyde-exposed workers were no higher than the rates among nonexposed coworkers. These results support the conclusion that airborne levels of 1 ppm time-weighted average and a 2 ppm ceiling provide adequate worker protection.

## OBJECTIVE

The study's objective was to determine whether occupational exposure to formaldehyde increases the Du Pont workers' risk of dying from cancer. Special interest was to center around cancers of the lung and upper respiratory tract, particularly the nasal cavities.

## BACKGROUND

The present study was initiated in 1980 after receipt of the preliminary results of a study by the Chemical Industry Institute of Toxicology (CIIT). The CIIT study was entitled: "A Chronic Toxicology Study in Rats and Mice Exposed to Formaldehyde."(1) According to the final CIIT report, rats and mice were exposed to 0, 2, 6, and 15 ppm of formaldehyde gas for six hours per day, 5 days per week for twenty-four months. At 15 ppm about 50% of the rats and 1% of the mice developed nasal cancer, primarily squamous cell carcinoma. One percent of the rats also developed nasal cancer at 6 ppm, but this number was not statistically significant $(p > 0.05)$. No nasal cancers were seen at 2 ppm or at 0 ppm.(2)

The carcinogenic response observed in the CIIT study was highly dependent on species, exposure level, and target tissue. Squamous cell carcinomas were observed only at exposure levels that were extremely irritating to the animals and that produced extensive cell destruction. This cell destruction was followed by rapid cell proliferation, increases in cell turnover rates, and squamous cell metaplasia. Metaplasia regressed in animals maintained 3 months after the 24-month exposure period.(2)

A Biodynamics chronic inhalation study exposed rats, monkeys, and hamsters to 3, 1, and 0.2 ppm formaldehyde for 22 hours per day for 6 months. No tissue damage was observed in hamsters at any of the exposure levels. Squamous cell metaplasia was observed in the nasal cavity of rats and monkeys exposed at 3 ppm. No tissue damage was observed at 1 ppm or below in rats and monkeys.(2)

Three epidemiologic studies specifically designed to assess the cancer risk from formaldehyde exposure in humans have shown no excesses of cancer that could be attributed to formaldehyde. These studies include the Walrath (National Cancer Institute) proportionate mortality study of New York morticians,(3) the Marsh (University of Pittsburgh) proportionate mortality study of formaldehyde resin plant workers,(4) and the Wong (Tabershaw Occupational Medicine Associates) cohort mortality study of formaldehyde manufacturing plant workers.(5)

Although there were no nasal cancer deaths observed in these three epidemiologic studies, some of the authors reported slight elevations in risks for certain other sites. The Walrath study found slight excesses for cancers of the skin, kidney and brain. Wong found slight excesses for prostatic and lymphopoietic cancers. Marsh on the other hand reported that rates for formaldehyde workers were "generally similar to those for unexposed workers".

When the results of the epidemiologic studies are viewed as a whole, the data suggest that formaldehyde has not been responsible for producing cancer in man. However, Wong's study was limited by small numbers. The proportionate mortality (PMR) studies of Marsh and Walrath were limited by the PMR design itself. Therefore, to help clarify the question concerning formaldehyde's effect in humans, Medical Division decided to conduct its own epidemiologic study of cancer risk among Du Pont formaldehyde workers.

## METHODS

### General Design

This was a matched-pairs case-control study of all male cancer deaths that occurred among active and pensioned employees at eight study plants from 1957 through 1979. For each cancer death, a control matched on age, payclass, sex, and adjusted service date (ASD) was chosen. Work histories and smoking histories were sought for all cases and controls. Jobs were categorized by frequency and intensity of exposure to formaldehyde. Estimates of relative risk (or odd ratios) were computed as measures of the cancer risk in formaldehyde-exposed workers relative to the risk in nonexposed workers.

### Study Populations

1. Plant Selection

The following plants were chosen to participate in the study:

| Plant/Dept. | Years formaldehyde was present | Approx. no. of past workers having had exposure |
|---|---|---|
| • Parlin (F&F) | 1940-1972 | 12 per year |
| • Belle (BIOCHEM) | 1939-present | unknown |
| • Parlin (PHOTO) | 1960-present | 300-400 |
| • Perth Amboy (ELECTROCH) | 1920-1970 | 20 per year |
| • Rochester (PHOTO) | 1945-present | 1000 |
| • Toledo (C&P) | 1947-present | 50-60 |
| • Toledo (F&F) | 1945-present | 30 per year |
| • Washington Works (PPD) | 1960-present | unknown |

There were several criteria for including a plant in the study:

- There must have been at least 15 years since formaldehyde was first used at the plant.
- The plant's use of formaldehyde must have been on a continuous basis.
- Recent exposure levels must have occasionally been at the odor threshold or above.
- The plant must have had a stable population.

### 2. Definition and selection of cases

Cases were defined as all male cancer deaths that occurred among active and pensioned employees at the study plants during the period 1957-1979. Only those cases for whom work histories could be ascertained were included in the study. Females were excluded from the study because the formaldehyde exposed work force was primarily male.

### 3. Definition and selection of controls

Each cancer case was matched with one male employee who was on the Company's active rolls during the case's last year of employment. To be eligible for selection, the control had to match the case's age (± 3 years), adjusted service date (± 3 years), plant location (exact), sex (males only), and payclass (wage or salary) as of the case's last year at the plant. For any given case the control was the first eligible employee appearing on the payroll roster after the case's name.

### 4. Definition of exposure

Within each plant, jobs were divided into three exposure categories: continuous-direct, intermittent, and background. These categories were based on both the frequency and intensity of exposure without regard to the use of respirators. Since routine use of respirators began only within the past 2 to 5 years, respirator usage did not complicate the exposure estimates.

- Continuous-direct exposure

  These were jobs in which a worker was assigned to a discrete area in which formaldehyde was produced, separated, recovered, processed, or loaded/unloaded. Exposure to formaldehyde must have occurred at least three days out of five to be included in this group.

Within this group, air exposures were ranked according to their approximate eight-hour time-weighted average concentrations:

Level 1 = $<$ 0.1 ppm.
Level 2 = 0.1 - 2.0 ppm.
Level 3 = $\geq$ 2.0 ppm.

The actual ppm values associated with each level were extrapolated from air monitoring data whenever possible. When air monitoring data were unavailable, long-service employees were able to recall certain acute effects associated with formaldehyde exposure, such as odor or sensory irritation (eye, nose, or throat).

- Intermittent exposure

These were jobs in which a worker was not assigned to a discrete area where formaldehyde was produced, separated, recovered, processed, or loaded/unloaded. However, the job required that the worker periodically work in these areas. These jobs were further divided into two exposure categories.

Low - jobs having little potential for permitting peak exposures to formaldehyde of the order of 2 ppm.

High- jobs permitting a worker to be exposed to peak formaldehyde concentrations of the order of 2 ppm or more.

The intermittent category typically included maintenance personnel assigned on a plant-wide basis, and laboratory quality control people who supported non-formaldehyde as well as formaldehyde units. The formaldehyde-exposed workers not falling into the continuous-direct category were placed into the intermittent category.

- Background exposure (nonexposed group)

These were all jobs that did not fall into the continuous-direct or intermittent groups.

Sources of data

1. Cancer deaths (cases)

All deaths among active and pensioned employees were identified through the Company's Mortality File. This file was begun in 1957 and was current at the time of this analysis through December, 1979. The Epidemiology Section's trained nosologists code each cause of death according to the ICD revision in effect at the time of death. The Company's noncontributory group life insurance plan is the mechanism by which deaths are reported in the mortality file.

## 2. Controls

Eligible controls were selected from annual plant payroll rosters that are kept on file in Wilmington Medical Division. These annual payroll rosters include all active employees at a plant during a given year. Wage roll employees appear on separate lists from salary roll employees. The lists are ordered by location and department, either alphabetically or by birth year.

## 3. Work histories

Work histories on all cases and controls were supplied by the plants. These histories for the large majority of subjects were obtained directly from personnel records. When personnel records were unavailable, medical records and interviews with co-workers were used to ascertain the work histories. When work history data were ascertained through interviews, long-service co-workers who had knowledge of both the worker and of the jobs with potential formaldehyde exposure were consulted.

The work history data that were collected on each case and control included:

- Name
- Social Security Number
- Sex
- Birth date
- Date hired
- Payclass when hired
- Final payclass
- Date of final departure from the plant
- Reason for departure
- All jobs held at the plant, including dates in and out of these jobs

- Work history prior to working at Du Pont, if available
- The formaldehyde exposure potential for each of the Du Pont jobs held.

This information was abstracted from plant personnel records, transcribed to code sheets (Appendix A), and forwarded to Wilmington Medical Division.

4. Assessment of formaldehyde exposure potential

Prior to assessing exposure potentials, the plant's industrial hygienists and other similarly qualified personnel were asked to complete three items: process descriptions, job code dictionaries and exposure potential dictionaries.

- Process descriptions included descriptions of the site's present and past processes, work areas, and jobs with potential formaldehyde exposures.
- Job code dictionary: Formaldehyde-associated work areas and jobs were defined, tabulated, and assigned numeric codes.
- Exposure potential dictionary:

Jobs by work area and time period were assigned to the exposure categories of continuous-direct, intermittent, or background. Continuous-direct jobs were further subdivided into levels 1-3, and intermittent jobs were subdivided into levels 1-2 (see exposure definitions given above).

Exposure potentials were extrapolations based on:

- Recent air monitoring data for current jobs and work areas. The Company's current airborne formaldehyde standard is a 1 ppm 8-hour TWA with a 2 ppm ceiling.
- Past air monitoring data from 5-7 years ago.
- Statements by long-service employees as to whether and how often formaldehyde was present in high enough concentrations to produce an odor or sensory irritation.
- Knowledge of odor and sensory irritation thresholds. The thresholds for odor recognition and sensory irritation vary considerably among individuals. The former has been reported at concentrations between 0.1 and 1 ppm, while sensory irritation is generally not reported until concentrations approach 0.5 to 1 ppm. As concentrations rise above 2 to 5 ppm, there will be definite complaints of eye, nose, and throat irritation.

- Knowledge of past process changes and of engineering or personal controls.

5. Smoking histories

Smoking histories of cases and controls were ascertained primarily by proxy, that is by interviewing subjects' living co-workers. In a few instances living controls were either interviewed directly, or smoking habits were ascertained from existing medical records.

All proxies were long-service active or pensioned employees who had either supervised the subject, worked in the same area, or been a close friend of the subject.

By reviewing personnel records and by questioning other long-service employees, plant personnel determined which co-workers were best suited to serve as proxies.

The proxy-completed questionnaires (Appendix B) allowed the cases and controls to be ranked according to the number of packs of cigarettes smoked per day (none, less than 1/2, 1/2-1, 1-2, 2 or more packs/day). Completed smoking history questionnaires were forwarded to Wilmington Medical Division for processing.

## Data processing and quality control

All smoking and work histories were abstracted from plant data sources and were transcribed to code sheets by plant personnel. These code sheets were then forwarded to Wilmington Medical Division for processing. Each plant also forwarded personnel records for several cases and controls. These records were checked against the completed code sheets to verify that the coding was accurate and complete.

The smoking and work history data were entered directly from code sheets into computer files. Computer routines were written to check for missing or invalid entries and to edit the data base. For all cases and controls the computer's version of the data was checked against the original code sheets for accuracy.

## Data analysis

In this study the relative odds ratio was used as the measure of association between exposure and disease. The relative odds ratio is the ratio of the odds of a case having been exposed relative to the odds of a control having been exposed. An odds ratio of 1.0 indicates no association.

For rare diseases such as lung or nasal cancer, the relative odds ratio closely approximates the relative risk ratio, another measure of association between exposure and disease. The relative risk ratio is the ratio of the exposed group's risk of dying from cancer relative to the nonexposed group's risk of dying from cancer. The terms relative risk ratio and relative odds ratio have been used interchangeably in this study.

Occasionally the term adjusted odds ratio was used. An adjusted odds ratio refers to an odds ratio that takes potentially confounding variables into account. The adjusted odds ratio was an age-, sex-, payclass-, ASD-, and plant site-adjusted odds ratio. When adjusted odds ratios were computed for lung cancer, they were also adjusted for differences in smoking habits. The adjustments for matching and smoking habits were done by the conditional logistic regression method of Breslow and Day.(6)

Adjusted odds ratios, lower and upper 95% confidence limits on these odds ratios, and two-tailed p-values were computed for all analyses. However, for descriptive purposes and ease of understanding, in most instances only crude (i.e., nonadjusted) odds ratios were presented. For the present data set, the differences between crude and adjusted odds ratios were small.

The data have been analyzed by:

- Tumor site (major organs and systems)
- Latency
- Duration
- Frequency of exposure (intermittent vs continuous)
- Exposure level
- Cumulative exposure index
- Year of death
- Age at death
- Age at first exposure
- Year at first exposure

Each cancer site was analyzed once for each of six different hypothetical latent periods: 0-4, 5-14, 15-24, 20+, and 25+ years. In subsequent analyses only latent periods that maximized the odds ratio in these initial analyses were used. Such an approach tends to minimize exposure misclassification that results from misspecification of the latent period. However, it also tends to slightly bias the analyses towards overestimating the true odds ratio.

Latency and exposure were treated in the following manner. A history of formaldehyde exposure was counted only if it occurred during a certain time period prior to the case's death. For instance, when a latent period of 20+ years was assumed, only exposure that occurred 20 or more years prior to the case's death was counted. This means that for controls, only exposure that occurred 20 or more years prior to the matching case's death was counted. Furthermore, formaldehyde exposure that occurred in a control after the matching case's death was ignored.

In all instances two-tailed significance tests were performed, and significance was judged at the 0.05 probability level.

## RESULTS

### Demographic description of cases and controls

From 1957 through 1979 there were 493 cancer deaths associated with the eight study plants (Table 1). Of these 493 cases 12 (2.5%) had to be excluded because work histories were unavailable. The twelve excluded cases consisted of 6 lung, 4 digestive, 1 lymphopoietic, and 1 other/unspecified cancer death. For about 2% of the cases a second control had to be chosen because work histories were unavailable for the first control chosen.

The distribution of cancer deaths by tumor site was not unusual (Table II). The tumor sites with the largest number of cases were lung (181), colon and rectum (54), lymphopoietic (49), prostate (33), and stomach (23). There was only 1 case in the category of nose, nasal cavities, eustachian tube and middle ear. This case was actually a eustachian tube/middle ear cancer, not a nasal cancer.

The distribution of cancer deaths by age group was about as expected (Table III). Lung, colon and rectum, lymphopoietic, and stomach were most common in the 60-69 year age group, whereas prostate was most common in the 70-79 year age group. Because an age-matched control was selected from each case, the average ages of cases (65.1 years) and controls (64.4 years) were very similar.

The ratio of wage to salary cases was about 3 to 1 (Table IV), which corresponds roughly to the actual wage/salary ratio for the plant populations. The number of cases increased steadily from 98 in the period 1957-1964 to 142 in the period 1975-1979 (Table V). This increase reflects a shift in the age distribution and an increase in the number of active and retired employees.

The prevalence of cigarette smoking (Table VI) was higher among cases than among controls. The all-cancer adjusted odds ratio of workers who smoked 2 or more packs of cigarettes per day relative to those who never smoked was 3.5. Smoking habits were unknown or unreported for about 10% of cases and controls. About 22% of the cases and 38% of the controls were nonsmokers.

With respect to lung cancer, only 12% of cases were nonsmokers compared to 36% of controls. The risk of lung cancer in smokers relative to nonsmokers showed a strong dose-response relationship. The adjusted odds ratio increased from 2.1 in those who smoked less than 1/2 pack/day to 10.3 in those who smoked 2 or more packs/day (Table VII).

## Odds ratios by latent period

The adjusted odds ratios generally showed little variation from one latent period to another (Table VIII). The one exception was for prostatic cancer, which had an odds ratio that was appreciably higher in the 15-24 year period than in the other periods.

Since most sites were slightly higher in the 15-24 or in the 20+ year period, these two periods were chosen for all subsequent analyses. The 20+ year latent period was chosen for cancers of the buccal cavity, esophagus, liver, lung, skin (melanoma), stomach, and bladder. The 15-24 year latent period was chosen for cancers of the pancreas, larynx, prostate, lymphopoietic system, brain, bone, colon and rectum, kidney, and all other ill-defined/unspecified sites.

Odds ratios were computed only for those sites with 7 or more cases. The one tumor that fell into the nose/nasal cavity/eustachian tube/middle ear category occurred in a worker who had no history of exposure to formaldehyde. As mentioned above, this worker's tumor was a eustachian tube/middle ear tumor rather than a nasal cancer.

## Duration of exposure

To see if cancer risk varied with duration of exposure, subjects with any exposure potential were classified as to whether they had worked around formaldehyde for less than 5 years, or for 5 years or more. Exposure duration was calculated after allowing for a latent period between exposure and disease (see Methods section).

The data showed no significant relationships between exposure duration and the relative odds ratios (Tables IX and X). None of the odds ratios was significantly higher than 1.0. However, the cancer odds ratio for prostate (Table IX, OR = 4.8) and bladder (Table X, OR=7.0) were slightly elevated in the 5 or more year duration category.

## Frequency of exposure: continuous vs intermittent

The risks of continuous and intermittent exposures relative to no exposure were assessed in Tables XI and XII. For no cancer site was the odds ratio significantly higher than 1.0 for either continuous or intermittent exposure categories.

## Frequency and level of exposure

The potential for formaldehyde exposure was further defined according to levels of exposure within the intermittent and continuous categories. The data showed no pattern of increasing risk with increasing dose (Tables XIII and XIV). Because of the large number of exposure categories, these and subsequent analyses were restricted to tumor sites with 5 or more exposed cancer deaths. Continuous level 3 was combined with continuous level 2 since there were only 2 cases and 2 controls in the level 3 category.

## Cumulative exposure index

As a means of simultaneously examining exposure duration and exposure level, a cumulative exposure index (CEI) was computed for each case and control. CEI was computed as the product of the exposure duration and exposure level. Duration of exposure was computed after allowing for a latent period (see Methods). Level of exposure was an exposure rank assigned to a given exposure category. The ranks used to compute the CEI were as follows:

| Exposure Category | Rank |
|---|---|
| Background | 0 |
| Intermittent #1 | 2 |
| Intermittent #2 | 4 |
| Continuous #1 | 1 |
| Continuous #2 | 3 |
| Continuous #3 | 5 |

The data showed no significant relationships between CEI and cancer risk. As in the analyses of exposure duration, the odds ratios for prostatic (OR=3.6) and bladder (OR=5.2) cancers were slightly but not significantly higher than 1.0 for the>20 CEI category (Tables XV and XVI).

## Year of death

Sometimes cancer risks will show trends with time that reflect dates of introduction or changing usage patterns of a physical agent. To investigate this possibility, the data were split into 5-year calendar periods.

No significant trends with time were observed (Table XVII). For this and subsequent analyses, only two sites were presented: lung and prostate. Lung was included because it was a site of special interest given the results of the CIIT study in rats. Prostate was presented because this was the site that in this study has shown the strongest although statistically nonsignificant relationship to formaldehyde exposure.

## Age of death

Sometimes a carcinogen may accelerate spontaneously occurring biologic processes so as to produce cancer at younger ages than usual but to cause little or no increase in overall cancer rates. To determine if risks were unusually high in younger age groups, the data were split into two groups according to the case's age at death.

The odds ratios in younger age groups were not significantly different from the odds ratios in older age groups (Table XVIII). There was no tendency for odds ratios to be higher in younger as opposed to older age groups.

## Year of first exposure

An analysis by year of first exposure will sometimes reveal unusually high risks for workers who were first exposed during a certain time interval. Such excesses may reflect dates of introduction or changes in exposure patterns for a physical agent.

When the formaldehyde data were analyzed by year of first exposure, no increasing or decreasing trends in time were noted for lung or prostate cancer risk (Table XIX).

## Age at first exposure

Certain investigators have suggested that humans may be more susceptible to the effects of carcinogens at earlier ages than at later ages. To assess this possibility the data have been analyzed according to age at first exposure.

There was no suggestion that relative risk was higher among workers first exposed at earlier ages than among those first exposed at later ages (Table XIX). In fact, controls tended to be first exposed at earlier ages than were the cases.

## Interaction with smoking habits

There have been a number of reports indicating that tobacco use can act in combination with other hazardous agents in the work place to produce or increase the severity of a wide variety of adverse health effects. The asbestos-smoking-lung cancer relationship is the most publicized example of this interaction.

To investigate the possibility of interaction between smoking, formaldehyde, and lung cancer, an interaction (cross product) term was introduced into the logistic analysis. The results of this analysis showed no evidence for an interaction between smoking and formaldehyde.

When the analyses were restricted to moderate and heavy smokers (Table XX), smoking formaldehyde workers showed no significant difference in lung cancer rates when compared to smoking coworkers who were not exposed to formaldehyde.

## Plant site-specific analyses

Plant site-specific analyses (Tables XXI and XXII) showed that no plant's overall cancer or lung cancer odds ratio for formaldehyde exposure was significantly greater than 1.0. That is, for any given plant the overall cancer risk in formaldehyde workers was not significantly higher than the risk in nonexposed coworkers.

## DISCUSSION

The significance of these results is better appreciated after a discussion of the study's strengths and potential limitations.

## Strengths

### a. Sensitivity

In a statistical sense, the study was very sensitive to increases in lung cancer and overall cancer risks among exposed workers. In fact, the study's sensitivity was comparable to what could be expected from a cohort study of 2650 formaldehyde workers followed for at least 20 years.

- The study had an 80% chance of detecting at least a 1.5-fold increase in overall cancer if formaldehyde indeed caused such an excess (Table XXIII).

- The study had an 80% chance of detecting at least a 2.3-fold excess of lung cancer among workers with 5 or more years of exposure if formaldehyde had indeed caused such an excess (Table XXIV).

— ? WHAT CHANCE OF DETECTING ↑ NASAL CA — NOT MUCH OR THEY WOULD HAVE STATED IT.

b. Internal comparisons

The case-control study by design compared cancer risk in formaldehyde-exposed workers to cancer risk in nonexposed co-workers. Furthermore, the study compared only workers who were of the same birth cohort, geographic area, plant site, payclass, and adjusted service date. Thus, this study was not subject to the uncertainties characteristic of many other studies concerning the importance of the healthy worker effect or of geographic, socioeconomic, or temporal differences in cancer rates.

c. Smoking habits

Cigarette smoking habits were ascertained by co-worker proxy for cases and control. This feature allowed the potential confounding effects of cigarette smoking habits to be reduced so that the relative risks of formaldehyde alone could be assessed. This adjustment for smoking habits greatly strengthened our conclusions concerning the relationship between lung cancer and formaldehyde exposure.

The validity of the smoking histories was supported by the strong dose-response relationship found for lung cancer and cigarette smoking (Table VII). This relationship was similar to what has been found nationally in cohort studies of smoking and lung cancer.

d. Exposure frequency, intensity, and duration

The data were such that meaningful comparisons could be made for frequency, intensity, and duration of exposure. Forty percent of exposed workers fell into the continuous exposure category, 60% fell into the intermittent exposure category. Two-thirds of the continuous exposure category had been exposed at 0.1 ppm or above, and 45% of the intermittent exposure category had been exposed at 2 ppm or about.

e. Adequate latent period

First exposures to formaldehyde occurred far enough in the past to allow for an adequate latent period. About 45% of the exposed cases and controls were first exposed prior to the

1940's when formaldehyde levels in many instances were higher than they are today. All of these workers had at least a 17-year latent period from the time of first exposure until death from cancer. Many had longer latent periods. Thus, the negative findings of this study cannot be said to be due to too short a latent period.

## Limitations

### a. Low sensitivity for extremely rare cancers

The study had limited sensitivity for cancer sites for which there were only a few cases. Even so, the observation that there were no formaldehyde-exposed nasal cancers in this study or in other studies permits us to establish an upper limit on the possible risk of nasal cancer from formaldehyde exposure.

EXAGGERATED CLAIM.

### b. Nonpensioned terminations, transfers

Cancer deaths among employees who left the Company without a pension or who transferred to a plant not in the study were not included in the study. These exclusions might comprise about 15-20% of the underlying work force. The exclusion of these subjects would bias the results only if the reasons for leaving the plant were related both to past exposures and to the risk of dying from cancer.

Even if these conditions were met, the extent of the bias was most likely minimal. A quantitative analysis of this situation showed that cancer risks in formaldehyde workers excluded from the study would have to be 5 to 10 times higher than the risk in those included before there would be a noticeable effect on the study's results. In short, it is unlikely that the exclusion of nonpensioned terminations and transfers could account for the study's negative findings.

- DUBIOUS ASSUMPTION
- POTENTIALLY SERIOUS OMISSION.

### c. Mixed exposures

At all of the study plants workers were exposed to a variety of materials in addition to formaldehyde. These mixed exposures could be viewed as a strength or as a limitation of the study.

With respect to the issue of synergism between formaldehyde and other chemicals, the presence of mixed exposures was a strength. In this study the cancer risk among workers exposed both to formaldehyde and to other chemicals was no higher than the risk in coworkers with no formaldehyde exposure. This finding suggests that synergism between formaldehyde and other materials in the work place is not a problem.

On the other hand, mixed exposures could have been a limitation if cancer risks in workers not exposed to formaldehyde were unusually high due to exposures to other occupational carcinogens. If formaldehyde were a carcinogen, nonformaldehyde workers' exposures to other carcinogens could have masked the effects of formaldehyde.

Haskell Laboratory has performed risk assessments on several materials that are used at the study plants. These materials are listed in Appendix C.

### d. Cancer mortality vs incidence

Since cancer deaths rather than incident cases were studied, the issue of survival rates becomes important. For cancers such as lung or pancreas, the survival rates are so poor that a study of mortality usually leads to the same conclusions as a study of incidence. For sites such as skin in which survival is very good, excesses of cancer incidence may not be accompanied by a corresponding increase in cancer mortality. The five-year survival rate for nasal cancer, which is about 45%, is intermediate between the survival rates for lung and skin cancer, so that an increase in nasal cancer incidence should be reflected by a subsequent increase in its mortality.

### e. Qualitative misclassification of exposure

Qualitative misclassification of exposure could have biased the study's results and caused either an overestimate or underestimate of the odds ratio. The direction and extent of this bias depends on the nature and degree of the misclassification.

An analysis of the situation showed that even if misclassification were as high as 5-10%, it was very unlikely that the bias could have been extensive enough to account for finding no association between formaldehyde and cancer.

### f. Quantitative misclassification of exposure

Estimates of exposure levels were based in part on air monitoring data from current working conditions. However, our knowledge of past process changes, engineering controls, odor and sensory irritation thresholds, and anecdotal reports by long-service employees suggest that formaldehyde levels were higher in the past than they are today.

When exposure levels were assigned to the various jobs, there may have been a tendency to emphasize current conditions and de-emphasize the past. Such a tendency could have caused systematic underestimates of the levels to which formaldehyde workers were exposed.

g. Smoking histories from proxies

Smoking histories of cases and controls were primarily ascertained through co-worker proxies. The ideal source of smoking history is the worker himself. If proxies must be used, the subject's next of kin are generally preferred. Co-workers will usually be unfamiliar with a subject's off-the-job smoking habits and with some of the finer details of his smoking history.

Despite this limitation, the study's lung cancer data showed a strong dose-response relationship with the amount smoked per day. This finding suggests that the smoking data were good enough to remove most of the confounding effects of cigarette smoking.

## Significance

The CIIT study suggested that if formaldehyde were a human carcinogen, then the upper respiratory tract, particularly the nasal cavities, were the most likely targets in humans. Some critics have argued that the lower respiratory tract should also be considered a likely target, since rats are obligate nose breathers but man is not.

The present study and three other epidemiology studies (Wong,(5) Walrath,(3) and Marsh(4)) of workers exposed to formaldehyde have found no excess risks for cancers of the nasal cavities, respiratory tract, or buccal cavity that could be attributed to formaldehyde exposure.

Although Wong(5) found a slight excess for lymphomas, and Walrath(3) found slight excesses for skin, kidney, and brain cancers, these excesses were not confirmed by the present study. Little importance should be attached to the positive findings in the Walrath study, since it was proportionate mortality (PMR) and subject to the limitations common to all PMR studies. Furthermore, Walrath's reported excess of skin cancers was obtained only after several histologic types with differing etiology were combined.

Wong(5) found a slight excess of prostate cancer among exposed workers. Coincidentally, cancer of the prostate was one of two sites in the present study that showed slight although statistically nonsignificant elevations in the odds ratio. The bladder was the other site that showed a slight excess.

We believe that the slight elevations in the prostatic and bladder cancer odds ratios found in the present study are chance occurrences and are unrelated to the workers' exposure to formaldehyde. The observations leading to this conclusion are as follows:

- The data suggest that by chance the controls chosen for prostate cases were not representative of the underlying control population with respect to formaldehyde exposure. The slight excesses observed for prostate appear to be due to under-representation of exposure in controls, not over-representation of exposure in cases.

  For example, only 9% of the prostate's controls were exposed whereas 20% of all controls were exposed. The exposure distribution for prostate cases, on the other hand, was similar to that found for all cancer cases and for their controls. Twenty-four percent of prostate cases were exposed vs 21% of all cancer cases.

- Neither the Walrath nor the Marsh study showed an elevated risk for either cancer of the prostate or bladder.

- Our analyses assumed latent periods that were designed to maximize the observed relative risk ratios. This treatment of latent period may have tended to overestimate the true relative risk.

- The elevations in risk were based on small numbers of cases and were subject to considerable statistical variability. Even so, all of the odds ratios were within the limits of sampling variation and were consistent with a true odds ratio of 1.0.

- The prostate cases came from six plants, the bladder cases from five plants. No one plant showed risks that were particularly higher than the others even though past formaldehyde levels were higher in some plants than in others.

- Prostate and bladder cancers are biologically unlikely sites for the action of formaldehyde, given that the target site in animal studies was restricted to the upper respiratory tract, specifically the nasal cavity.

- The study was subject to the multiple comparison problem and should be interpreted accordingly. That is, any epidemiologic study of this size presents the investigator with a multitude of possible comparisons. A long series of comparisons will, with high probability, result in some comparisons testing significant, even in the absence of any causal relationships.

  In this study the probability that at least one comparison would show a significant difference simply on the basis of chance was better than 40%.

## Conclusions

The data have been analyzed by tumor site, latent period, duration of exposure, exposure level and frequency, cumulative exposure index, age and year of death, and age and year of first exposure. In none of these analyses was the relative risk (odds ratio) of cancer for exposed workers significantly greater than 1.0 based on standard statistical analyses.

There was only one cancer death in the category of nose, nasal cavity, or middle ear. This was not a nasal cancer, but rather was a cancer of the middle ear/eustachian tube. Furthermore, the case showed no history of occupational exposure to formaldehyde.

Cancer of the respiratory system showed no signs of being more common in formaldehyde workers than in nonexposed co-workers. The analyses for cancer of the lung were adjusted for cigarette smoking habits, so that the absence of an association between formaldehyde and lung cancer was unlikely to be due to the confounding effects of cigarette smoking.

In short, a thorough analysis of the data suggested that cancer mortality rates in the Company's formaldehyde-exposed workers were no higher than the rates among nonexposed coworkers. These results support the position that airborne formaldehyde levels of 1 ppm TWA and a 2 ppm ceiling provide adequate worker protection.

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TABLE I: NUMBERS OF CANCER DEATHS IN EACH PLANT

| Plant site | # Cancer deaths 1957-79 | # Cancer deaths 1957-79 that were included in the study * |
|---|---|---|
| Parlin F&F | 87 | 79 (1) |
| Belle | 220 | 218 (2) |
| Parlin Photo | 83 | 83 |
| Perth Amboy | 10 | 10 |
| Rochester Photo | 35 | 35 |
| Toledo C&P | 3 | 3 |
| Toledo F&F | 19 | 19 |
| Washington Works | 36 | 34 (3) |
| Total | 493 | 481 |

[*] A total of twelve cases were dropped from the study because work histories were unavailable for these cases.

(1) Work histories could not be determined for 4 lung cancer deaths, 3 digestive cancer deaths, and for 1 other/unspecified cancer death.

(2) Work histories could not be determined for 1 lung cancer death and for 1 digestive cancer death.

(3) Work histories could not be determined for 1 lung cancer death and for 1 lymphopoietic cancer death.

### TABLE II: DISTRIBUTION OF CANCER DEATHS BY PLANT SITE AND TUMOR SITE

| TUMOR SITE | PARLIN F&F | PARLIN PHOTO | TOLEDO F&F | TOLEDO C&P | PERTH AMBOY | ROCHESTER PHOTO | BELLE BIOCH | WASHINGTON WORKS PPD | TOTAL |
|---|---|---|---|---|---|---|---|---|---|
| -Buccal cavity, pharynx | 2 | 1 | 0 | 0 | 0 | 1 | 2 | 1 | 7 |
| -Esophagus | 1 | 0 | 1 | 0 | 0 | 3 | 4 | 0 | 9 |
| -Stomach | 7 | 7 | 0 | 0 | 3 | 2 | 4 | 0 | 23 |
| -Small intestine | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| -Colon and rectum | 12 | 13 | 1 | 0 | 0 | 4 | 20 | 4 | 54 |
| -Liver, gall bladder | 1 | 2 | 0 | 0 | 0 | 0 | 5 | 2 | 10 |
| -Pancreas | 5 | 7 | 0 | 0 | 0 | 0 | 4 | 2 | 18 |
| -Eustachian tube/middle ear | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| -Larynx | 3 | 0 | 1 | 0 | 0 | 1 | 3 | 0 | 8 |
| -Lung, bronchus | 19 | 20 | 10 | 2 | 4 | 10 | 104 | 12 | 181 |
| -Other respiratory | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| -Pleura | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| -Prostate | 4 | 5 | 2 | 0 | 1 | 2 | 19 | 0 | 33 |
| -Testis | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 3 |
| -Other genital | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 3 |
| -Kidney | 0 | 3 | 0 | 0 | 0 | 1 | 9 | 0 | 13 |
| -Bladder | 2 | 2 | 1 | 0 | 0 | 1 | 4 | 0 | 10 |
| -Lymphopoietic | 5 | 11 | 2 | 0 | 0 | 5 | 22 | 4 | 49 |
| -Brain, other nervous | 2 | 4 | 0 | 0 | 0 | 1 | 4 | 1 | 12 |
| -Connective tissue | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| -Malignant melanoma | 2 | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 7 |
| -Other skin | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| -Other endocrine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| -Bone | 3 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 7 |
| -All other ill-defined/ unspecified | 6 | 1 | 1 | 1 | 1 | 3 | 9 | 2 | 24 |
| -Peritoneum, retroperit. | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| -All sites | 79 | 83 | 19 | 3 | 10 | 35 | 218 | 34 | 481 |

TABLE III: DISTRIBUTION OF CANCER DEATHS BY AGE GROUP AND TUMOR SITE

| | | | | | | Average age (years | |
|---|---|---|---|---|---|---|---|
| Cause of death by tumor site | <50 | 50-59 | 60-69 | 70-79 | 80+ | Case | Control |
| Buccal cavity, pharynx | 0 | 2 | 2 | 3 | 0 | 67.0 | 66.6 |
| Esophagus | 0 | 1 | 5 | 2 | 1 | 66.6 | 66.4 |
| Stomach | 0 | 7 | 9 | 5 | 2 | 64.9 | 64.5 |
| Small intestine | 0 | 0 | 1 | 0 | 0 | 61.0 | 62.0 |
| Colon and rectum | 0 | 8 | 29 | 14 | 3 | 66.7 | 66.1 |
| Liver, gall bladder | 0 | 1 | 4 | 3 | 2 | 69.7 | 68.9 |
| Pancreas | 1 | 2 | 10 | 3 | 2 | 66.7 | 63.5 |
| Peritoneum, retroperit | 0 | 0 | 0 | 0 | 1 | 82.0 | 82.0 |
| Eustachian tube,middle ear | 1 | 0 | 0 | 0 | 0 | 37.0 | 37.0 |
| Larynx | 0 | 0 | 6 | 1 | 1 | 68.8 | 67.9 |
| Lung, bronchus, trachea | 9 | 46 | 76 | 43 | 7 | 63.7 | 62.8 |
| Other/ill-defined resp. | 0 | 0 | 2 | 0 | 0 | 68.5 | 67.5 |
| Pleura | 0 | 0 | 0 | 0 | 1 | 83.0 | 81.0 |
| Prostate | 0 | 0 | 7 | 18 | 8 | 74.4 | 74.2 |
| Testis | 1 | 1 | 1 | 0 | 0 | 56.3 | 56.0 |
| Other male genital | 1 | 0 | 1 | 1 | 0 | 61.0 | 61.0 |
| Kidney | 0 | 2 | 6 | 5 | 0 | 67.6 | 68.0 |
| Bladder | 1 | 0 | 4 | 4 | 1 | 67.7 | 68.0 |
| Lymphopoietic | 4 | 12 | 15 | 14 | 4 | 64.5 | 63.4 |
| Brain | 4 | 5 | 2 | 1 | 0 | 52.5 | 52.7 |
| Connective tissue | 1 | 1 | 0 | 0 | 0 | 49.5 | 48.5 |
| Malignant melanoma | 2 | 2 | 1 | 2 | 0 | 59.1 | 59.4 |
| Other skin | 1 | 0 | 0 | 0 | 0 | 61.0 | 60.0 |
| Other endocrine | 0 | 1 | 0 | 0 | 0 | 50.0 | 50.0 |
| Bone | 2 | 1 | 1 | 2 | 1 | 63.9 | 63.1 |
| All other ill-defined/unspec. | 1 | 5 | 11 | 6 | 1 | 64.8 | 65.0 |
| All tumor sites | 28 | 97 | 194 | 127 | 35 | 65.1 | 64.4 |

TABLE IV: DISTRIBUTION OF CANCER DEATHS BY PAYCLASS AND TUMOR SITE

| Cause of death by tumor site | Wage | Salary |
|---|---|---|
| Buccal cavity, pharynx | 6 | 1 |
| Esophagus | 6 | 3 |
| Stomach | 19 | 4 |
| Small intestine | 0 | 1 |
| Colon and rectum | 41 | 13 |
| Liver, gall bladder | 9 | 1 |
| Pancreas | 10 | 8 |
| Peritoneum, retroperit | 1 | 0 |
| Eustachian tube, middle ear | 0 | 1 |
| Larynx | 7 | 1 |
| Lung, bronchus, trachea | 141 | 40 |
| Other/ill-defined resp. | 2 | 0 |
| Pleura | 1 | 0 |
| Prostate | 25 | 8 |
| Testis | 3 | 0 |
| Other male genital | 3 | 0 |
| Kidney | 12 | 1 |
| Bladder | 8 | 2 |
| Lymphopoietic | 32 | 17 |
| Brain | 11 | 1 |
| Connective tissue | 1 | 1 |
| Malignant melanoma | 7 | 0 |
| Other skin | 0 | 1 |
| Other endocrine | 1 | 0 |
| Bone | 6 | 1 |
| All other ill-defined/unspec. | 15 | 9 |
| All tumor sites | 367 | 114 |

### TABLE V: DISTRIBUTION OF CANCER DEATHS BY YEAR OF DEATH AND BY TUMOR SITE

| Cause of death by tumor site | 1957-64 | 1965-69 | 1970-74 | 1975-79 |
|---|---|---|---|---|
| Buccal cavity, pharynx | 2 | 3 | 1 | 1 |
| Esophagus | 1 | 1 | 3 | 4 |
| Stomach | 7 | 4 | 7 | 5 |
| Small intestine | 0 | 0 | 1 | 0 |
| Colon and rectum | 13 | 8 | 17 | 16 |
| Liver, gall bladder | 2 | 1 | 5 | 2 |
| Pancreas | 7 | 1 | 3 | 7 |
| Peritoneum, retroperit | 0 | 0 | 0 | 1 |
| Eustachian tube, middle ear | 1 | 0 | 0 | 0 |
| Larynx | 0 | 4 | 2 | 2 |
| Lung, bronchus, trachea | 27 | 46 | 50 | 58 |
| Other/ill-defined resp. | 0 | 1 | 0 | 1 |
| Pleura | 0 | 0 | 0 | 1 |
| Prostate | 4 | 6 | 13 | 10 |
| Testis | 0 | 1 | 2 | 0 |
| Other male genital | 1 | 0 | 1 | 1 |
| Kidney | 4 | 2 | 3 | 4 |
| Bladder | 3 | 2 | 2 | 3 |
| Lymphopoietic | 6 | 11 | 16 | 16 |
| Brain | 5 | 4 | 3 | 0 |
| Connective tissue | 1 | 1 | 0 | 0 |
| Malignant melanoma | 2 | 1 | 2 | 2 |
| Other skin | 1 | 0 | 0 | 0 |
| Other endocrine | 0 | 1 | 0 | 0 |
| Bone | 4 | 0 | 3 | 0 |
| All other ill-defined/unspec. | 7 | 5 | 4 | 8 |
| All tumor sites | 98 | 103 | 138 | 142 |

TABLE VI: ALL CANCER DEATHS, 1957-1979: ADJUSTED ODDS RATIOS* ACCORDING TO CIGARETTE SMOKING HABITS ASCERTAINED FROM LIVING COWORKERS

| Cigarette Smoking Status (Packs/Day) | #Cases | #Controls | Crude Odds Ratio | Adjusted Odds Ratio | Lower 95% Confidence Limit | Upper 95% Confidence Limit | Two-Tailed P-Value |
|---|---|---|---|---|---|---|---|
| Nonsmoker | 107 | 181 | 1.00 | 1.00 | ----- | ----- | ----- |
| 0 - 1/2 or exsmoker | 44 | 67 | 1.11 | 1.10 | 0.68 | 1.77 | 0.71 |
| 1/2 - 1 | 148 | 108 | 2.32 | 2.53 | 1.72 | 3.72 | $<0.01$ |
| 1 - 2 | 65 | 45 | 2.44 | 2.25 | 1.44 | 3.53 | $<0.01$ |
| 2 or more | 58 | 30 | 3.27 | 3.49 | 2.05 | 5.93 | $<0.01$ |
| Current, amount? | 11 | 8 | 2.33 | 2.04 | 0.79 | 5.27 | 0.14 |
| Unknown | 48 | 42 | 1.93 | 1.92 | 1.08 | 3.39 | 0.03 |
| TOTAL | 481 | 481 | | | | | |

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[*] Odds ratios were adjusted for the matched-pairs design. The adjustment was carried out by the conditional logistic regression method for matched pairs (Breslow and Day, 1981).

TABLE VII: ALL LUNG, BRONCHUS, AND TRACHEA CANCER DEATHS, 1957-1979: ADJUSTED ODDS RATIOS* ACCORDING TO CIGARETTE SMOKING HABITS ASCERTAINED FROM LIVING COWORKERS

| Cigarette Smoking Status (Packs/Day) | #Cases | #Controls | Crude Odds Ratio | Adjusted Odds Ratio | Lower 95% Confidence Limit | Upper 95% Confidence Limit | Two-Tailed P-Value |
|---|---|---|---|---|---|---|---|
| Nonsmoker | 22 | 66 | 1.00 | 1.00 | ----- | ----- | ----- |
| 0 - 1/2 or exsmoker | 21 | 30 | 2.10 | 2.19 | 0.94 | 5.10 | 0.07 |
| 1/2 - 1 | 62 | 45 | 4.13 | 5.01 | 2.33 | 10.74 | < 0.01 |
| 1 - 2 | 26 | 16 | 4.88 | 4.38 | 1.85 | 10.35 | < 0.01 |
| 2 or more | 27 | 10 | 8.10 | 10.34 | 3.66 | 29.19 | < 0.01 |
| Current, amount? | 5 | 2 | 7.50 | 5.55 | 0.93 | 33.26 | 0.06 |
| Unknown | 18 | 12 | 4.50 | 7.01 | 1.99 | 24.66 | < 0.01 |
| TOTAL | 181 | 181 | | | | | |

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*Odds ratios were adjusted for the matched-pairs design. The adjustment was carried out by the conditional logistic regression method for matched pairs (Breslow and Day, 1981).

## TABLE VIII: ADJUSTED* RELATIVE ODDS RATIOS BY TUMOR SITE AND EXPOSURE PERIOD PRIOR TO THE CASE'S DEATH FOR CASES OCCURRING DURING THE INTERVAL 1957-1979

| Cause of death by tumor site*** | # Cases | Exposure period (in years prior to the case's death)** | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0-4 | 5-14 | 15-24 | 25+ | 15+ | 20+ |
| Buccal cavity, pharynx | 7 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Esophagus | 9 | 0.00 | 1.00 | 0.00 | 0.50 | 1.00 | 1.00 |
| Stomach | 23 | 0.67 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Colon and rectum | 54 | 0.44 | 0.54 | 0.75 | 0.50 | 0.69 | 0.45 |
| Liver, gall bladder, biliary passages | 10 | ---- | >1 | 0.50 | 1.00 | 0.50 | 0.50 |
| Pancreas | 18 | 0.50 | 0.50 | 1.00 | 0.00 | 0.00 | 0.00 |
| Larynx | 8 | 0.00 | 1.00 | 1.00 | 0.00 | 2.00 | 0.00 |
| Lung, bronchus, trachea | 181 | 1.28 | 0.89 | 1.14 | 1.28 | 1.29 | 1.46 |
| Prostate | 33 | 0.00 | 3.00 | 6.00 | 1.67 | 2.50 | 2.50 |
| Kidney | 13 | 1.00 | 1.00 | 2.00 | >1 | 2.00 | 1.00 |
| Bladder | 10 | >1 | >1 | >1 | >1 | >1 | >1 |
| Lymphopoietic | 49 | 0.00 | 0.67 | 0.67 | 0.50 | 0.50 | 0.60 |
| Brain | 12 | 0.25 | 0.00 | 0.50 | 0.00 | 0.50 | 0.00 |
| Malignant melanoma | 7 | ---- | 1.00 | 1.00 | ---- | 0.00 | 1.00 |
| Bone | 7 | 2.00 | 2.00 | 2.00 | 1.00 | 2.00 | 1.00 |
| Other ill-defined, unspecified | 24 | 1.00 | 1.00 | 1.67 | 0.33 | 0.83 | 0.67 |
| All sites | 481 | 0.78 | 0.86 | 1.03 | 0.84 | 0.95 | 0.85 |

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[*] Odds ratios were adjusted for the matched pairs design. Lung, bronchus and trachea cancer were also adjusted for cigarette smoking habits.

[**] In this analysis only exposure that occurred in the specified period prior to death of the case is considered to be relevant.

[***] In this analysis only tumor sites with more than three cases were included.

## TABLE IX: CANCER DEATHS AT STUDY PLANTS, 1957-1979[*] CRUDE ODDS RATIOS[@] ACCORDING TO NUMBER OF YEARS EMPLOYEE WORKED AROUND FORMALDEHYDE: LATENT PERIOD = 15-24 YEARS

| | # Cases | # Controls | Odds Ratio |
|---|---|---|---|
| **Pancreas** | | | |
| None | 16 | 16 | 1.00 |
| Less than 5 | 0 | 0 | ---- |
| 5 or more | 2 | 2 | 1.00 |
| **Larynx** | | | |
| None | 6 | 6 | 1.00 |
| Less than 5 | 2 | 1 | 2.00 |
| 5 or more | 0 | 1 | 0.00 |
| **Prostate** | | | |
| None | 25 | 30 | 1.00 |
| Less than 5 | 0 | 1 | 0.00 |
| 5 or more | 8 | 2 | 4.80 |
| **Lymphopoietic system** | | | |
| None | 43 | 41 | 1.00 |
| Less than 5 | 2 | 6 | 0.32 |
| 5 or more | 4 | 2 | 1.91 |
| **Brain and other nervous systsm** | | | |
| None | 11 | 10 | 1.00 |
| Less than 5 | 1 | 0 | ---- |
| 5 or more | 0 | 2 | 0.00 |

| | # Cases | # Controls | Odds Ratio |
|---|---|---|---|
| **Bone** | | | |
| None | 4 | 5 | 1.00 |
| Less than 5 | 1 | 0 | ---- |
| 5 or more | 2 | 2 | 1.25 |
| **All other ill-defined/unspecified** | | | |
| None | 18 | 20 | 1.00 |
| Less than 5 | 1 | 0 | ---- |
| 5 or more | 5 | 4 | 1.39 |
| **Colon and rectum** | | | |
| None | 42 | 39 | 1.00 |
| Less than 5 | 4 | 3 | 1.24 |
| 5 or more | 8 | 12 | 0.62 |
| **Kidney** | | | |
| None | 11 | 12 | 1.00 |
| Less than 5 | 1 | 0 | ---- |
| 5 or more | 1 | 1 | 1.09 |
| **All sites** | | | |
| None | 381 | 383 | 1.00 |
| Less than 5 | 33 | 29 | 1.14 |
| 5 or more | 67 | 69 | 0.98 |

[*] Analyses are restricted to sites with 7 or more cancer deaths.

[@] Odds ratios estimate risk of less than 5 years exposure and 5 or more years exposure relative to the risk of no exposure.

TABLE X: CANCER DEATHS AT STUDY PLANTS, 1957-1979*
CRUDE ODDS RATIOS@ ACCORDING TO NUMBER OF YEARS EMPLOYEE
WORKED AROUND FORMALDEHYDE: LATENT PERIOD = 20+ YR.

| | # Cases | # Controls | Odds Ratio | | # Cases | # Controls | Odds Ratio |
|---|---|---|---|---|---|---|---|
| Buccal cavity | | | | Malignant melanoma | | | |
| None | 6 | 6 | 1.00 | None | 6 | 6 | 1.00 |
| Less than 5 | 0 | 0 | ---- | Less than 5 | 1 | 1 | 1.00 |
| 5 or more | 1 | 1 | 1.00 | 5 or more | 0 | 0 | ---- |
| Esophagus | | | | Stomach | | | |
| None | 6 | 6 | 1.00 | None | 17 | 17 | 1.00 |
| Less than 5 | 2 | 1 | 2.00 | Less than 5 | 0 | 0 | ---- |
| 5 or more | 1 | 2 | 0.50 | 5 or more | 6 | 6 | 1.00 |
| Liver, Gall Bladder, Bile Duct | | | | Bladder | | | |
| None | 9 | 8 | 1.00 | None | 4 | 7 | 1.00 |
| Less than 5 | 0 | 1 | 0.00 | Less than 5 | 2 | 2 | 1.75 |
| 5 or more | 1 | 1 | 0.89 | 5 or more | 4 | 1 | 7.00 |
| Lung, Bronchus, Trachea | | | | All sites | | | |
| None | 142 | 142 | 1.00 | None | 387 | 377 | 1.00 |
| Less than 5 | 24 | 20 | 1.20 | Less than 5 | 39 | 46 | 0.83 |
| 5 or more | 15 | 19 | 0.79 | 5 or more | 55 | 58 | 0.92 |

*Analyses are restricted to sites with 7 or more cancer deaths.

@Odds ratios estimate risk of less than 5 years exposure and 5 or more years exposure relative to the risk of no exposure.

TABLE XI: CANCER DEATHS AT STUDY PLANTS, 1957-1979*
CRUDE ODDS RATIOS@ ACCORDING TO WHETHER EMPLOYEE HAD CONTINUOUS
OR INTERMITTENT FORMALDEHYDE EXPOSURE: LATENT PERIOD = 15-24 YEARS

|  | # Cases | # Controls | Odds Ratio |  | # Cases | # Controls | Odds Ratio |
|---|---|---|---|---|---|---|---|
| Pancreatic |  |  |  | Lymphopoietic |  |  |  |
| None (background) | 16 | 16 | 1.00 | None (background) | 43 | 41 | 1.00 |
| Continuous only | 1 | 1 | 1.00 | Continuous only | 3 | 3 | 0.95 |
| Intermittent only | 1 | 1 | 1.00 | Intermittent only | 3 | 5 | 0.57 |
| Larynx |  |  |  | Brain and other nervous |  |  |  |
| None (background) | 6 | 6 | 1.00 | None (background) | 11 | 10 | 1.00 |
| Continuous only | 2 | 1 | 2.00 | Continuous only | 0 | 1 | 0.00 |
| Intermittent only | 0 | 1 | 0.00 | Intermittent only | 1 | 1 | 0.91 |
| Prostatic |  |  |  | Bone |  |  |  |
| None (background) | 25 | 30 | 1.00 | None (background) | 4 | 5 | 1.00 |
| Continuous only | 2 | 1 | 2.40 | Continuous only | 1 | 0 | ---- |
| Intermittent only | 6 | 2 | 3.60 | Intermittent only | 2 | 2 | 1.25 |
| Kidney |  |  |  | All other ill-defined/unspecified |  |  |  |
| None (background) | 11 | 12 | 1.00 | None (background) | 18 | 20 | 1.00 |
| Continuous only | 0 | 0 | ---- | Continuous only | 3 | 2 | 1.67 |
| Intermittent only | 2 | 1 | 2.18 | Intermittent only | 3 | 2 | 1.67 |
| Colon and rectum |  |  |  | All sites |  |  |  |
| None (background) | 42 | 39 | 1.00 | None (background) | 381 | 383 | 1.00 |
| Continuous only | 4 | 5 | 0.74 | Continuous only | 36 | 35 | 1.03 |
| Intermittent only | 8 | 10 | 0.74 | Intermittent only | 62 | 61 | 1.02 |
|  |  |  |  | Cont. & intermit. | 2 | 2 | 1.01 |

*Analyses are restricted to sites with 7 or more cancer deaths.

@Odds ratios estimate risk of continuous exposure and of intermittent exposure relative to the risk of no exposure.

TABLE XII: CANCER DEATHS AT STUDY PLANTS, 1957-1979*
CRUDE ODDS RATIOS@ ACCORDING TO WHETHER EMPLOYEE HAD CONTINUOUS
OR INTERMITTENT FORMALDEHYDE EXPOSURE: LATENT PERIOD = 20 OR MORE YEARS

| | # Cases | # Controls | Odds Ratio |
|---|---|---|---|
| Buccal cavity | | | |
| None (background) | 6 | 6 | 1.00 |
| Continuous only | 0 | 0 | ---- |
| Intermittent only | 1 | 1 | ---- |
| Esophagus | | | |
| None (background) | 6 | 6 | 1.00 |
| Continuous only | 2 | 2 | 1.00 |
| Intermittent only | 1 | 1 | 1.00 |
| Stomach | | | |
| None (background) | 17 | 17 | 1.00 |
| Continuous only | 2 | 2 | 1.00 |
| Intermittent only | 3 | 4 | 1.00 |
| Cont. & intermit. | 1 | 0 | ---- |
| Liver, gall bladder, bile duct | | | |
| None (background) | 9 | 8 | 1.00 |
| Continuous only | 0 | 0 | ---- |
| Intermittent only | 1 | 2 | 0.44 |

| | # Cases | # Controls | Odds Ratio |
|---|---|---|---|
| Bladder | | | |
| None (background) | 4 | 7 | 1.00 |
| Continuous only | 3 | 1 | 5.25 |
| Intermittent only | 3 | 2 | 2.63 |
| Malignant melanoma | | | |
| None (background) | 6 | 6 | 1.00 |
| Continuous only | 1 | 0 | ---- |
| Intermittent only | 0 | 0 | ---- |
| Cont. & intermitt. | 0 | 1 | 0.00 |
| Lung, bronchus, trachea | | | |
| None (background) | 142 | 142 | 1.00 |
| Continuous only | 17 | 14 | 1.21 |
| Intermittent only | 22 | 24 | 0.92 |
| Cont. & intermit. | 0 | 1 | 0.00 |
| All sites | | | |
| None (background) | 387 | 387 | 1.00 |
| Continuous only | 39 | 32 | 1.19 |
| Intermittent only | 54 | 70 | 0.75 |
| Cont. & intermitt. | 1 | 2 | 0.49 |

*Analyses are restricted to sites with 7 or more cancer deaths.

@Odds ratios estimate risk of continuous exposure and of intermittent exposure relative to the risk of no exposure.

### TABLE XIII: CANCER DEATHS AT STUDY PLANTS, 1957-1979:*
### CRUDE ODDS RATIOS ACCORDING TO WHETHER EMPLOYEE HAD INTERMITTENT (LEVELS 1-2) OR CONTINUOUS (LEVELS 1-3) FORMALDEHYDE EXPOSURE--LATENT PERIOD = 15-24 YEARS

| | # Cases | # Controls | Odds Ratio |
|---|---|---|---|
| **Colon & rectum** | | | |
| None (background) | 42 | 39 | 1.00 |
| Intermittent #1 | 3 | 5 | 0.56 |
| Intermittent #2 | 5 | 4 | 1.16 |
| Continuous #1 | 2 | 1 | 1.86 |
| Continuous #2/#3 | 1 | 3 | 0.31 |
| Mixed | 1 | 2 | 0.46 |
| **Lymphopoietic system** | | | |
| None (background) | 43 | 41 | 1.00 |
| Intermittent #1 | 2 | 3 | 0.64 |
| Intermittent #2 | 1 | 2 | 0.48 |
| Continuous #1 | 2 | 0 | ---- |
| Continuous #2/#3 | 1 | 3 | 0.32 |
| Mixed | 0 | 0 | ---- |
| **Other ill-defined/unspecified sites** | | | |
| None (background) | 18 | 20 | 1.00 |
| Intermittent #1 | 0 | 1 | 0.00 |
| Intermittent #2 | 3 | 1 | 3.33 |
| Continuous #1 | 1 | 0 | ---- |
| Continuous #2/#3 | 1 | 2 | 0.56 |
| Mixed | 1 | 0 | ---- |

| | # Cases | # Controls | Odds Ratio |
|---|---|---|---|
| **Prostate** | | | |
| None (background) | 25 | 30 | 1.00 |
| Intermittent #1 | 4 | 2 | 2.40 |
| Intermittent #2 | 2 | 0 | ---- |
| Continuous #1 | 1 | 0 | ---- |
| Continuous #2 | 1 | 1 | ---- |
| Mixed | 0 | 0 | ---- |
| **All sites** | | | |
| None (background) | 381 | 383 | 1.00 |
| Intermittent #1 | 35 | 36 | 0.98 |
| Intermittent #2 | 27 | 23 | 1.18 |
| Continuous #1 | 10 | 7 | 1.44 |
| Continuous #2 | 18 | 23 | 0.79 |
| Continuous #3 | 2 | 2 | 1.01 |
| Mixed | 8 | 7 | 1.15 |

---

Intermittent #1: $<$2.0 ppm.
Intermittent #2: $\geq$2.0 ppm.
Continuous #1: $<$0.1 ppm.
Continuous #2: 0.1 – 2.0 ppm.
Continuous #3: $\geq$2.0 ppm.
Mixed: exposure occurred in more than one exposure category.

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[*] Analyses are restricted to sites with 5 or more exposed cancer deaths.

## TABLE XIV: CANCER DEATHS AT STUDY PLANTS, 1957-1979:* CRUDE ODDS RATIOS ACCORDING TO WHETHER EMPLOYEE HAD INTERMITTENT (LEVELS 1-2) OR CONTINUOUS (LEVELS 1-3) FORMALDEHYDE EXPOSURE--LATENT PERIOD = 20 OR MORE YEARS

|  | # Cases | # Controls | Odds Ratio |
|---|---|---|---|
| **Lung** |  |  |  |
| None (background) | 142 | 142 | 1.00 |
| Intermittent #1 | 14 | 16 | 0.88 |
| Intermittent #2 | 8 | 5 | 0.88 |
| Continuous #1 | 5 | 3 | 1.67 |
| Continuous #2/#3 | 11 | 10 | 1.10 |
| Mixed | 1 | 5 | 0.20 |
| **Bladder** |  |  |  |
| None (background) | 4 | 7 | 1.00 |
| Intermittent #1 | 1 | 1 | 1.75 |
| Intermittent #2 | 1 | 0 | ---- |
| Continuous #1 | 0 | 0 | ---- |
| Continuous #2/#3 | 2 | 1 | 3.50 |
| Mixed | 2 | 1 | 3.50 |

|  | # Cases | # Controls | Odds Ratio |
|---|---|---|---|
| **Stomach** |  |  |  |
| None (background) | 17 | 17 | 1.00 |
| Intermittent #1 | 3 | 2 | 1.50 |
| Intermittent #2 | 0 | 2 | 0.00 |
| Continuous #1 | 0 | 1 | 0.00 |
| Continuous #2/#3 | 1 | 1 | 1.00 |
| Mixed | 2 | 0 | ---- |
| **All sites** |  |  |  |
| None (background) | 387 | 377 | 1.00 |
| Intermittent #1 | 30 | 43 | 0.68 |
| Intermittent #2 | 20 | 19 | 1.03 |
| Continuous #1 | 11 | 8 | 1.34 |
| Continuous #2/#3 | 21 | 23 | 0.89 |
| Mixed | 12 | 11 | 1.06 |

---

Intermittent # 1: $\leq$ 2.0 ppm.
Intermittent # 2: $\geq$ 2.0 ppm.
Continuous #1: $<$ 0.1 ppm.
Continuous #2: 0.1 – 2.0 ppm.
Continuous #3: $\geq$ 2.0 ppm.

Mixed: exposure occurred in more than one exposure category.

[*] Analyses are restricted to sites with 5 or more exposed cancer deaths.

## TABLE XV: CANCER DEATHS AT STUDY PLANTS, 1957-1979[@]: CRUDE ODDS RATIOS FOR FORMALDEHYDE EXPOSURE AS MEASURED BY THE CUMULATIVE EXPOSURE INDEX (CEI)[*] -- LATENT PERIOD = 15-24 YEARS

| | # Cases | # Controls | Odds Ratio | | # Cases | # Controls | Odds Ratio |
|---|---|---|---|---|---|---|---|
| Colon and rectum | | | | Prostate | | | |
| 0 (background only) | 42 | 39 | 1.00 | 0 (background only) | 25 | 30 | 1.00 |
| ≤20 | 6 | 8 | 0.70 | ≤20 | 5 | 2 | 3.00 |
| >20 | 6 | 7 | 0.80 | >20 | 3 | 1 | 3.60 |
| Lymphopoietic system | | | | All sites | | | |
| 0 (background only) | 43 | 41 | 1.00 | 0 (background only) | 381 | 383 | 1.00 |
| ≤20 | 5 | 7 | 0.68 | ≤20 | 65 | 62 | 1.05 |
| >20 | 1 | 1 | 0.95 | >20 | 35 | 36 | 0.98 |

[@] Analyses are restricted to sites with 5 or more exposed cancer deaths.

[*] Cumulative exposure (CEI) = no. years in a given exposure category x rank of that category.

Formaldehyde exposure potentials were assigned the following ranks before the CEI was computed:

| Potential | Rank |
|---|---|
| Background | 0 |
| Interm. #1 | 2 |
| Interm. #2 | 4 |
| Continuous #1 | 1 |
| Continuous #2 | 3 |
| Continuous #3 | 5 |

## TABLE XVI: CANCER DEATHS AT STUDY PLANTS, 1957-1979:[@] CRUDE ODDS RATIOS FOR FORMALDEHYDE EXPOSURE AS MEASURED BY THE CUMULATIVE EXPOSURE INDEX (CEI)* -- LATENT PERIOD = 20 OR MORE YEARS

|  | # Cases | # Controls | Odds Ratio |  | # Cases | # Controls | Odds Ratio |
|---|---|---|---|---|---|---|---|
| Lung, bronchus |  |  |  | Stomach |  |  |  |
| 0 (background only) | 142 | 142 | 1.00 | 0 (background only) | 17 | 17 | 1.00 |
| ≤20 | 27 | 25 | 1.08 | ≤20 | 1 | 1 | 1.00 |
| >20 | 12 | 14 | 0.86 | >20 | 5 | 5 | 1.00 |
| Bladder |  |  |  | All sites |  |  |  |
| 0 (background only) | 4 | 7 | 1.00 | 0 (background only) | 387 | 377 | 1.00 |
| ≤20 | 3 | 2 | 2.63 | ≤20 | 48 | 58 | 0.81 |
| >20 | 3 | 1 | 5.25 | >20 | 46 | 46 | 0.97 |

---

[@] Analyses are restricted to sites with 5 or more exposed cancer deaths.

[*] Cumulative exposure (CEI) = no. years in a given exposure category x rank of that category.

Formaldehyde exposure potentials were assigned the following ranks before the CEI was computed:

| Potential | Rank |
|---|---|
| Background | 0 |
| Interm. #1 | 2 |
| Interm. #2 | 4 |
| Continuous #1 | 1 |
| Continuous #2 | 3 |
| Continuous #3 | 5 |

## TABLE XVII: CANCER DEATHS AT STUDY PLANTS, 1957-1979: CRUDE ODDS RATIOS ACCORDING TO WHETHER EMPLOYEE EVER WORKED AROUND FORMALDEHYDE--DATA BROKEN DOWN BY YEAR OF DEATH--LATENT PERIOD = 20+ YEARS FOR LUNG CANCER, 15-24 YEARS FOR PROSTATIC CANCER AND ALL CANCER

| | 1957-64 | | | 1965-69 | | | 1970-74 | | | 1975-79 | | | 1957-79 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. Case | No Contr | Odds Ratio | No. Case | No. Contr | Odds Ratio | No. Case | No. Contr | Odds Ratio | No. Case | No. Contr | Odds Ratio | No. Case | No. Contr | Odds Ratio |
| Lung, bronchus | | | | | | | | | | | | | | | |
| Background | 23 | 23 | 1.00 | 37 | 35 | 1.00 | 41 | 40 | 1.00 | 41 | 44 | 1.00 | 142 | 142 | 1.00 |
| Ever exposed | 4 | 4 | 1.00 | 9 | 11 | 0.77 | 9 | 10 | 0.88 | 17 | 14 | 1.30 | 39 | 39 | 1.00 |
| Prostate | | | | | | | | | | | | | | | |
| Background | 4 | 4 | 1.00 | 5 | 6 | 1.00 | 10 | 12 | 1.00 | 6 | 8 | 1.00 | 25 | 30 | 1.00 |
| Ever exposed | 0 | 0 | ---- | 1 | 0 | ---- | 3 | 1 | 3.60 | 4 | 2 | 2.67 | 8 | 3 | 3.20 |
| All sites | | | | | | | | | | | | | | | |
| Background | 79 | 73 | 1.00 | 83 | 81 | 1.00 | 114 | 114 | 1.00 | 105 | 115 | 1.00 | 381 | 383 | 1.00 |
| Ever exposed | 19 | 25 | 0.70 | 20 | 22 | 0.89 | 24 | 24 | 1.00 | 37 | 27 | 1.50 | 100 | 98 | 1.03 |

TABLE XVIII: CANCER DEATHS AT STUDY PLANTS, 1957-1979:
CRUDE ODDS RATIOS ACCORDING TO WHETHER EMPLOYEE EVER WORKED
AROUND FORMALDEHYDE--DATA BROKEN DOWN BY AGE AT DEATH--LATENT
PERIOD = 20+ YEARS FOR LUNG CANCER, 15-24 YEARS FOR PROSTATIC CANCER AND ALL CANCER

| | Ages 20-64 years | | | Ages 65 years or older | | |
|---|---|---|---|---|---|---|
| | No. Cases | No. Controls | Odds Ratio | No. Cases | No. Controls | Odds Ratio |
| Lung, bronchus | | | | | | |
| Background | 83 | 80 | 1.00 | 59 | 62 | 1.00 |
| Ever exposed | 22 | 25 | 0.85 | 17 | 14 | 1.28 |
| Prostate | | | | | | |
| Background | 2 | 2 | 1.00 | 23 | 28 | 1.00 |
| Ever exposed | 1 | 1 | 1.00 | 7 | 2 | 4.26 |
| All sites | | | | | | |
| Background | 185 | 180 | 1.00 | 196 | 203 | 1.00 |
| Ever exposed | 50 | 55 | 0.88 | 50 | 43 | 1.20 |

TABLE XIX: CANCER DEATHS 1957 - 1979 : ODDS RATIOS
ACCORDING TO YEAR AND AGE OF FIRST FORMALDEHYDE EXPOSURE

| --Year First Exposed-- | # Cases | # Controls | Crude Odds Ratio | --Age (in years) First Exposed-- | # Cases | # Controls | Crude Odds Rat |
|---|---|---|---|---|---|---|---|
| Lung, bronchus | | | | Lung, bronchus | | | |
| Never exposed | 119 | 122 | 1.00 | Never exposed | 119 | 122 | 1.00 |
| Prior to 1940 | 7 | 3 | 2.39 | Less than 30 years | 8 | 9 | 0.91 |
| 1940 - 1949 | 17 | 26 | 0.67 | 30 - 39 years | 13 | 16 | 0.83 |
| 1950 - 1959 | 23 | 12 | 1.96 | 40 - 49 years | 23 | 18 | 1.31 |
| 1960 - 1979 | 15 | 18 | 0.85 | 50 or over | 18 | 16 | 1.15 |
| Prostate | | | | Prostate | | | |
| Never exposed | 24 | 27 | 1.00 | Never exposed | 24 | 27 | 1.00 |
| Prior to 1940 | 2 | 1 | 2.25 | Less than 30 years | 1 | 2 | 0.56 |
| 1940 - 1949 | 4 | 3 | 1.50 | 30 - 39 years | 1 | 1 | 1.13 |
| 1950 - 1959 | 3 | 1 | 3.38 | 40 - 49 years | 3 | 1 | 3.38 |
| 1960 - 1979 | 0 | 1 | 0.00 | 50 or over | 4 | 2 | 2.25 |
| All sites | | | | All sites | | | |
| Never exposed | 339 | 328 | 1.00 | Never exposed | 339 | 328 | 1.00 |
| Prior to 1940 | 22 | 19 | 1.12 | Less than 30 years | 19 | 26 | 0.71 |
| 1940 - 1949 | 40 | 50 | 0.77 | 30 - 39 years | 32 | 38 | 0.81 |
| 1950 - 1959 | 58 | 49 | 1.15 | 40 - 49 years | 48 | 43 | 1.08 |
| 1960 - 1979 | 22 | 35 | 0.61 | 50 or over | 43 | 46 | 0.90 |

## TABLE XX:

## LUNG, BRONCHUS, AND TRACHEA CANCER DEATHS, ALL AGES, 1957-1979: CRUDE ODDS RATIOS ACCORDING TO WHETHER EMPLOYEE EVER WORKED AROUND FORMALDEHYDE -- MODERATE AND HEAVY CIGARETTE SMOKERS ONLY *

| FORMALDEHYDE EXPOSURE POTENTIAL | NO. CASES | NO. CONTROLS | ODDS RATIO |
|---|---|---|---|
| BACKGROUND ONLY | 91 | 59 | 1.0 |
| EVER EXPOSED | 24 | 12 | 1.3 |
| TOTAL | 115 | 71 | |

* This analysis is restricted to cases and controls known to have smoked at least 1 pack of cigarettes per day.

## TABLE XXI:
## ALL CANCER DEATHS AT STUDY PLANTS, 1957-1979 -- CRUDE ODDS RATIOS BY PLANT ACCORDING TO EVER VS NEVER EXPOSED TO FORMALDEHYDE: LATENT PERIOD = 20 + YEARS

| PLANT SITE | NO. CASES | NO. CONTROLS | ODDS RATIO |
|---|---|---|---|
| PARLIN F&F | | | |
| BACKGROUND | 59 | 60 | 1.0 |
| EXPOSED | 20 | 19 | 1.1 |
| BELLE | | | |
| BACKGROUND | 196 | 188 | 1.0 |
| EXPOSED | 22 | 30 | 0.7 |
| PARLIN PHOTO | | | |
| BACKGROUND | 64 | 58 | 1.0 |
| EXPOSED | 19 | 25 | 0.7 |
| TOLEDO F&F | | | |
| BACKGROUND | 8 | 9 | 1.0 |
| EXPOSED | 11 | 10 | 1.2 |
| TOLEDO C&P | | | |
| BACKGROUND | 3 | 1 | 1.0 |
| EXPOSED | 0 | 2 | <1.0 |
| PERTH AMBOY | | | |
| BACKGROUND | 3 | 3 | 1.0 |
| EXPOSED | 7 | 7 | 1.0 |
| ROCHESTER PHOTO | | | |
| BACKGROUND | 21 | 24 | 1.0 |
| EXPOSED | 14 | 11 | 1.5 |
| WASHINGTON WORKS | | | |
| BACKGROUND | 33 | 34 | 1.0 |
| EXPOSED | 1 | 0 | --- |

### TABLE XXII:

### LUNG CANCER DEATHS AT STUDY PLANTS, 1957-1979 -- CRUDE ODDS RATIOS BY PLANT ACCORDING TO EVER VS NEVER EXPOSED TO FORMALDEHYDE: LATENT PERIOD = 20 + YEARS

| PLANT SITE | NO. CASES | NO. CONTROLS | ODDS RATIO |
|---|---|---|---|
| PARLIN F&F | | | |
| BACKGROUND | 14 | 13 | 1.0 |
| EXPOSED | 5 | 6 | 0.8 |
| BELLE | | | |
| BACKGROUND | 87 | 89 | 1.0 |
| EXPOSED | 17 | 15 | 1.2 |
| PARLIN PHOTO | | | |
| BACKGROUND | 14 | 14 | 1.0 |
| EXPOSED | 6 | 6 | 1.0 |
| TOLEDO F&F | | | |
| BACKGROUND | 4 | 4 | 1.0 |
| EXPOSED | 6 | 6 | 1.0 |
| TOLEDO C&P | | | |
| BACKGROUND | 2 | 0 | 1.0 |
| EXPOSED | 0 | 2 | <1.0 |
| PERTH AMBOY | | | |
| BACKGROUND | 2 | 3 | 1.0 |
| EXPOSED | 2 | 1 | 3.0 |
| ROCHESTER PHOTO | | | |
| BACKGROUND | 7 | 7 | 1.0 |
| EXPOSED | 3 | 3 | 1.0 |
| WASHINGTON WORKS | | | |
| BACKGROUND | 12 | 12 | 1.0 |
| EXPOSED | 0 | 0 | --- |

TABLE XXIII:

SENSITIVITY OF THE FORMALDEHYDE STUDY BY TUMOR SITE:
THE SMALLEST DETECTABLE RELATIVE ODDS RATIOS FOR WORKERS
EVER EXPOSED TO FORMALDEHYDE--LATENT PERIOD = 20+ YEARS

| Cause of death by tumor site | # Cases | # Controls | Smallest detectable odds ratio 80% Power(1) | Smallest detectable odds ratio 90% Power(1) |
|---|---|---|---|---|
| Buccal cavity, pharynx | 7 | 7 | 30.7 | 65.8 |
| Esophagus | 9 | 9 | 18.0 | 29.5 |
| Stomach | 23 | 23 | 5.9 | 7.5 |
| Colon and rectum | 54 | 54 | 3.3 | 3.9 |
| Liver, gall bladder, biliary passages | 10 | 10 | 15.1 | 23.4 |
| Pancreas | 18 | 18 | 7.3 | 9.7 |
| Larynx | 8 | 8 | 22.5 | 40.3 |
| Lung, bronchus, trachea | 181 | 181 | 2.0 | 2.2 |
| Prostate | 33 | 33 | 4.4 | 5.5 |
| Kidney | 13 | 13 | 10.5 | 14.8 |
| Bladder | 10 | 10 | 15.1 | 23.4 |
| Lymphopoietic | 49 | 49 | 3.5 | 4.1 |
| Brain | 12 | 12 | 11.6 | 16.8 |
| Malignant melanoma | 7 | 7 | 30.7 | 65.8 |
| Bone | 7 | 7 | 30.7 | 65.8 |
| Other ill-defined, unspecified | 24 | 24 | 5.6 | 7.2 |
| All sites | 481 | 481 | 1.5 | 1.6 |

(1) If the population odds ratio is at least as large as that given, the probability of declaring the sample odds ratio to be statistically significant is 0.80 for 80% power, 0.90 for 90% power. Statistical significance tests are assumed to be two-tailed, and significance is judged at the 0.05 probability level. Twenty percent of the controls are assumed to have been exposed to formaldehyde.

TABLE XXIV:

SENSITIVITY OF THE FORMALDEHYDE STUDY BY TUMOR SITE: THE SMALLEST DETECTABLE RELATIVE ODDS RATIOS FOR WORKERS EXPOSED FOR AT LEAST 5 YEARS--LATENT PERIOD = 20+ YEARS

| Cause of death by tumor site | # Cases | # Controls | Smallest detectable odds ratio for 80% power(1) |
|---|---|---|---|
| Buccal cavity, pharynx | 7 | 7 | 32.4 |
| Esophagus | 9 | 9 | 21.6 |
| Stomach | 23 | 23 | 7.7 |
| Colon and rectum | 54 | 54 | 4.2 |
| Liver, gall bladder, biliary passages | 10 | 10 | 18.7 |
| Pancreas | 18 | 18 | 9.7 |
| Larynx | 8 | 8 | 25.9 |
| Lung, bronchus, trachea | 181 | 181 | 2.3 |
| Prostate | 33 | 33 | 5.8 |
| Kidney | 13 | 13 | 13.6 |
| Bladder | 10 | 10 | 18.7 |
| Lymphopoietic | 49 | 49 | 4.4 |
| Brain | 12 | 12 | 14.9 |
| Malignant melanoma | 7 | 7 | 32.4 |
| Bone | 7 | 7 | 32.4 |
| Other ill-defined, unspecified | 24 | 24 | 7.5 |
| All sites | 481 | 481 | 1.7 |

(1) If the population odds ratio is at least as large as that given, the probability of declaring the sample odds ratio to be statistically significant is 0.80 for 80% power. Statistical significance tests are assumed to be two-tailed, and significance is judged at the 0.05 probability level. Ten percent of the controls are assumed to have been exposed to formaldehyde for at least 5 years.

APPENDIX A: FORMALDEHYDE STUDY CODE SHEET FOR WORK HISTORIES

S.S. No.: __ __ __-__ __-__ __ __ __

Case No.: __ __ __-__

Department Code

Plant Site Code

Birth date (month/year): __ __/__ __

Date hired (month/year): __ __/__ __

Initial payclass (1=wage, 2=salary): __

Final payclass (1=wage, 2=salary): __

Number of jobs listed below: __ __

C = Continuous-direct (C1, C2, or C3)
I = Intermittent (I1 or I2)
B = Background

List chronologically all jobs:

| Job | Area and Job Name | Area Code | Job Code | Date in (mo./yr.) | Date out (mo./yr.) | Exposure Category |
|---|---|---|---|---|---|---|
| 1. | | | | | | |
| 2. | | | | | | |
| 3. | | | | | | |
| 4. | | | | | | |
| 5. | | | | | | |
| 6. | | | | | | |
| 7. | | | | | | |
| 8. | | | | | | |
| 9. | | | | | | |
| 10. | | | | | | |
| 11. | | | | | | |
| 12. | | | | | | |
| 13. | | | | | | |
| 14. | | | | | | |
| 15. | | | | | | |
| 16. | | | | | | |
| 17. | | | | | | |
| 18. | | | | | | |

Last day at plant (month/year): __ __/__ __

Termination reason: 1 (still active) 2 (pensioned) 3 (resigned) 4 (deceased) 5 (T&P disability) 6 (transferred) 7 (Other)

Worker's name
(last, first, middle initial): __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

## APPENDIX B: SMOKING HISTORY QUESTIONNAIRE

Subject's name: ______________________________________________
Last First Middle initial

What is your relationship to the subject? ______________________
______________________________________________

The smoking history given below is based primarily on:

a. Your memory b. Medical records

If history is based primarily on your memory, how many years had you known the subject?

a. < 1 year
b. 1-5 years
c. 6-10 years
d. 11-15 years
e. > 15 years

When was the last time (e.g., 1968) that you saw the subject? 19___

With respect to cigarettes the subject was a:

a. Current smoker
b. Ex-smoker
c. Never smoked (never smoked as much as one cigarette per day for as long as one year)

If the subject was a current or ex-smoker:

When the subject smoked, he was a:

a. Light smoker
b. Moderate smoker
c. Heavy smoker
d. Don't know

How many packs per day did he smoke when he was a smoker?

a. Less than 1/2
b. 1/2 - 1
c. 1 - 2
d. 2 or more
e. Don't know

If he was an ex-smoker, in what year did he quit smoking? 19___

With respect to pipes, the subject was a:

a. Current smoker
b. Ex-smoker
c. Never smoker
d. Don't know

With respect to cigars, the subject was a:

a. Current smoker
b. Ex-smoker
c. Never smoked
d. Don't know

Name of person who filled out the above questionnaire.

(Please print): ______________________________________________

## APPENDIX C:

## MATERIALS THAT HAVE UNDERGONE RISK ASSESSMENT BY HASKELL LABORATORY - AND WHICH ARE FOUND AT THE FORMALDEHYDE STUDY PLANTS

### Washington Works (PPD)

Asbestos
Benzene*
Carbon tetrachloride*
Chloroform*
4-Dimethylaminobenzene
4-Aminodiphenyl
Dimethyl sulfate
p-Dioxane
Lead chromate
Tetrachloroethylene
B-propiolactone
Trichlorethylene
Zinc chromate
Freon-22

### Parlin (PHOTO)

Asbestos
Chloroform
Trichloroethylene
Tetrachloroethylene
ETU
Thiourea*
Benzene*

### Rochester (PHOTO)

Asbestos
Acrylonitrile*
3-amino-1,2,4-triazole
Ammonium perfluorooctanoate (C-8)
Carbon tetrachloride*
Freon-22
Chloroform*
Dimethyl formamide*
o-Dianisidine*
1,1-dimethyl hydrazine*
Dimethyl sulfate*
Dioxane*
Epichlorhydrin*
2-ethoxy ethanol
ETU*
Formamide*
Hydrazine*
Lead nitrate
Lead
Light green S-F dye
Tetramethyl thiourea*
Thioacetamide
Thiourea*
Toluene-2,4-diamine
o-Toluidine*

## APPENDIX C (continued):

## MATERIALS THAT HAVE UNDERGONE RISK ASSESSMENT BY HASKELL LABORATORY AND WHICH ARE FOUND AT THE FORMALDEHYDE STUDY PLANTS

Parlin (F&F)

Acrylonitrile
Asbestos
Benzene*
Propyleneimine
Carbon tetrachloride*
Chloroform*
Dioxane
Lead chromate
Lead molybdate
Strontium chromate
Trichloroethylene
Zinc chromate
Cadmium
Fuel oils

Toledo (F&F)

Acrylonitrile
Asbestos
Benzene*
Lead chromate
Lead molybdate
Strontium chromate
Zinc chromate
Cadmium
Fuel oils

Belle (BIOCHEM)

Asbestos
Benzene*
Dimethylnitrosamine*
Carbon tetrachloride*
Benomyl
MBC
Chloroform*
Dimethylacetamide
Dimethyl formamide
Dimethyl sulfate
1,4-Dioxane

Toledo (C&P)

None

* Present as impurity in trace amounts, used in laboratory, or used in R&D.

# APPENDIX 3

Excerpts of Todhunter
Pencil comments

Insert #1

The results of the CIIT bioassay are sufficient to establish that formaldehyde is an animal carcinogen. Based on the differences in response to exposure shown by rats and mice, different species may have differing sensitivities but this is a quantitative rather than a qualitative difference. It can be expected that under appropriate conditions of exposure that formaldehyde gas could pose a carcinogenic risk to humans.

Some findings of the CIIT research team have bearing on the interpretation of the positive bioassay results:

(1) At low levels of exposure or at short exposure times with higher levels of exposure the hyperplasia and metaplasia observed in response to exposure are reversible. This suggests that a higher exposure level or longer exposure time may produce a qualitatively different outcome with respect to carcinogenesis than would low level or short term exposures.

(2) The normal tissue levels of formaldehyde produced endogenously by metabolism range from 3 - 12 μg /g tissue wet weight (3-12 ppm). Much of this appears to be bound up as adducts to glutathione, tetrahydrofolate, and proteins. From 10% - 40% of the total tissue formaldehyde appears to exist as free formaldehyde ( 0.3 μg/g - 4.8 μg/g ). Spontaneous nasal carcinoma is unknown in the rat and there may, therefore,

be a natural or practical threshold for carcinogenesis induced by the endogenous metabolite. A sustained exposure of 3 ppm formaldehyde in air is needed to double the endogenous level of formaldehyde.

(3) There appears to be a threshold for cytotoxicity to the nasal mucosa at around 0.5 ppm exposure.

(4) Radio-tracer measurements indicate that absorption of formaldehyde gas from the inspired air is essentially complete within the nasal spaces and that formaldehyde gas does not reach the trachea or lungs at the exposure levels used in the CIIT study.

(5) Formaldehyde is a mutagen and a presumptive genotoxin. Aldehydes, as a chemical class, are also promoters (Slaga, T.J.; Sivak, A.; and Boutwell, R.K.; *Mechanisms of Tumor Promotion and Cocarcinogens*, Raven Press, N.Y., 1978). Formaldehyde can, then, be expected to both initiate and promote the carcinogenic process. This promoting and/or cocarcinogenic effect of formaldehyde is supported by other of the studies described in this *Technical Document* (vide infra). Since Promotion generally requires repeated, long term exposure to the promoter, is reversible (Weisburger, J.H. and Williams, G.M.; "*Chemical Carcinogenesis*" in Holland, J.F. and Frei, E. (eds): *Cancer Medicine*; 2nd ed. Lea + Febiger, Philadelphia, 1980) it may involve

damage to cellular components (Slaga et al, 1978), and is a requisite, at "some" point, for the carcinogenic process (Weisburger and Williams, 1980). When taken together with the observations reported by CIIT regarding the reversibility of the hyperplastic and metaplastic effects of formaldehyde (see (1) above) and a reported cytotoxicity threshold (see (3) above) the degree to which formaldehyde promotes its own carcinogenic effects may lead to qualitative differences in response to low levels or short exposures as opposed to high levels and long exposures.

The argument can be made that the initiating effects of formaldehyde would, none-the-less, produce a population of transformed, latent malignant cells. These cells would then produce malignancies in response to other promoters (endogenous or exogenous) as the animals grew older. In such a case the differences in response to formaldehyde over different portions of the dose response curve (which is markedly non-linear, see Fig ___) would be only quantitative and not qualitative. This argument is classical and has some merit. It needs to be discussed in the context of formaldehyde effects on the nasal mucosa.

Two points of reference which may be useful are that nasal carcinoma is not a known, naturally occurring tumor of the rat (the human incidence, in the United States, of this lesion is ca. 200-250 cases per year — i.e. $1 \times 10^{-6}$ — all off which appears to be associated with cigarette smoking) and that formaldehyde is an endogenous metabolite present in tissues at levels from 0.3 ppm – 4.8 ppm as free formaldehyde.

Clearly, in the absence of endogenous detoxifying mechanisms, the endogenous formaldehyde should be capable of initiating some cells. The observed absence or insignificant incidence of nasal carcinomas in rodents as spontaneous tumors indicates one of three things: (a) no cells are, in fact, initiated by endogenous levels of formaldehyde; (b) there are not endogenous promoters available to allow expression of the transformed cells; or (c) any cells initiated are sloughed off the epithelial layers before their malignant potential can be expressed.

The first situation (a) would, de facto, define a threshold for genotoxicity. Such a threshold could only exist if damage to DNA were efficiently repaired prior to replication of the affected cell. McCarthy has in fact demonstrated such genotoxicity thresholds for synchronized cells treated with α-benzpyrene or N-acetylaminofluorene (McCarthy, 1979). The degree to which similar effects can be seen in non-synchronous cell populations such as the epithelia of the nasal mucosa is not known. Certainly, repair mechanisms will be important in differentiated somatic tissues unless cell proliferation is stimulated. This is evidenced by the observation that tumors appear to arise from stem cell populations rather than from terminally differentiated somatic cell lines (Braun, 1972; Pitot, 1980). To the extent that a

[illegible] occurring [illegible] formaldehyde is localized subcellularly or otherwise sequestered, the cell will not see the formaldehyde.

The assumption that endogenous and exogenous formaldehyde are the same in relation to consequences to the cell is not necessarily valid.

material - such as formaldehyde - cause increased stem cell proliferation on exposure it is reasonable to expect that the dose/responce curve will be concave upward (i.e: disproportionately greater tumor responce at high doses) even if no discrete threshold is found.

The second situation (b) would require that promotion by exogenous factors was the controlling element in formaldehyde carcinogenesis. This would imply a lack of carcinogenic effects at exposures which did not produce promotion. The observation in the CIIT study that tumor formation is secondary to a formaldehyde induced hyperplasia and metaplasia does suggest that the promoting effects of formaldehyde may be quite important. As such, this situation would suggest qualitative changes in the response to formaldehyde exposure at low vs high concentrations.

The third situation (c) is probably very relevant to the question of formaldehyde carcinogenesis. The epithelia of the nasal mucosa normally slough off cells daily which are replaced by underlying cell layers. Thus cells initiated by formaldehyde (presumably derived from epithelial stem cells - i.e: undifferentiated fibroblasts) might be lost from the body before their malignant potential could be expressed.

The observed lack of spontaneous nasal carcinoma in rats - given the endogenous levels of formaldehyde present - is probably explained by a combination of these considerations. The net result is that there appears to be at least a practical threshold for the effects of formaldehyde.

Excerpts from Technical
Document of February 19,
1981, with changes

# PRIORITY REVIEW LEVEL 1: FORMALDEHDYE

February 19, 1981

DRAFT

Office of Toxic Substances
Office of Pesticides and Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

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turbinates and 3 respiratory epithelial tumors) were detected in rats (all unscheduled deaths and scheduled sacrifices through the 24-month sacrifice) exposed to 14.1 ppm formaldehyde. Three tumors also were detected at 24 months in rats exposed to 5.6 ppm formaldehyde.

The CIIT bioassay protocol was reviewed by a panel of experts convened by the Consumer Product Safety Commission (CPSC), under the aegis of the National Toxicology Program (NTP), and found to be consistent with accepted standards for conducting inhalation exposure bioassays. The NTP panel, using bioassay data available through the 18-month sacrifice (i.e., 36 squamous cell carcinomas of the nasal turbinates) concluded that "formaldehyde poses a cancer risk to humans". The panel did not comment as to the degree of risk posed by formaldehyde.

Using a linearized multistage carcinogenesis model, in conjunction with the available results from the CIIT bioassay and estimated levels of formaldehyde exposures for various subpopulations in the U.S., the upper 95% confidence limits on lifetime human carcinogenic risks were calculated. ~~The calculated risk estimates suggest that a high level of risk may be associated with a number of situations involving exposures to formaldehyde.~~ For most of the identified subpopulations, the estimated risks are equal to or greater than $10^{-5}$. ~~however, in some instances the risks are in the range of $10^{-1}$ (e.g., U-F foam producers/distributors exposed to 5.4 ppm , pathologists exposed to 7.9 ppm), $10^{-2}$ (e.g., workers in U-F foam insulated buildings exposed to 3.1 ppm U-F foam installers/dealers exposed to 2.4 ppm), and $10^{-3}$ (e.g.,~~ direct producers ~~of formaldehyde).~~ The reader, however, should note that these risk estimates are upper 95% confidence limits; i.e., risks generally will not exceed these estimates, but may, in fact, be considerably less.

usual [illegible] average exposure
instead of high [illegible]

Generally, the available information supports the view that formaldehyde has carcinogenic potential. That this potential poses a significant risk to humans is not supported by the evidence.

CODED / Background / Richard Dailey #1 Disk
Corrected on Disk

## I. BACKGROUND

The Chemical Industry Institute of Toxicology (CIIT) released preliminary information in October, 1979, which suggested that formaldehyde may induce cancer in rats following inhalation exposure. Information submitted to EPA under section 8(e) of the Toxic Substances Control Act (TSCA) by several formaldehyde producers stated that cancer had been found in three Fischer 344 rats in the CIIT study at the 15th month of a scheduled 24-month bioassay.

~~In light of the preliminary carcinogenicity data and the widespread potential for exposure to formaldehyde (evidenced in part by the large number of consumer complaints involving formaldehyde exposures that had been received by various Federal and State agencies) the Environmental Protection Agency (EPA) joined in a cooperative effort with other Federal agencies under the aegis of the Interagency Regulatory Liaison Group (IRLG) to perform a joint "integrated" risk assessment on formaldehyde. The integrated IRLG assessment, which addresses all potential sources of exposure to and effects of formaldehdye, is scheduled for completion in mid-1981.~~ aren't we past this? Was it delayed?

A later CIIT report released in January, 1980, revealed that by the scheduled 18-month sacrifice the number of nasal squamous cell carcinomas in formaldehyde-exposed animals had increased to a total of 36, as contrasted with no carcinomas in the control animals. Subsequently, the Consumer Product Safety Commission (CPSC), in conjunction with the National Toxicology Program (NTP), convened a panel of experts to review and evaluate the study protocol and preliminary results of the CIIT bioassay, as well as other available scientific literature on formaldehyde carcinogenicity. The panel report, issued November 21, 1980, concludes that "formaldehyde poses a cancer risk to humans". The degree of risk 'was' not discussed.

concentrations of monomeric formaldehyde (less than 0.1% (1,000 ppm), as reported above). Considering the rapid biodegradability and potential dilution effects of the receiving water, very low concentrations of formaldehyde would be expected in ambient waters, except in extreme cases such as spills of concentrated solutions.

## E. Monitoring Data

### 1. Introduction

This section discusses the levels of formaldehyde observed in air, water, soil, food, and consumer products. Most of the monitoring data in the literature concerns levels in either indoor or outdoor air. These data will be discussed first, followed by a discussion of data reported for other media. There are few quantitative data on the levels of formaldehyde in food or consumer products which allow a reliable estimation of exposure through ingestion or dermal routes. However, based on the information presented in section D (see exposure pathways and environmental fate of formaldehyde), the predominant potential exposure route is inhalation.

additional material inserted here by FED.

Table 4 is a summary of the inhalation-related monitoring data found in the literature. The following observations can be made from the table:

(1) Although most of the releases of formaldehyde are from inadvertent sources, the highest potential exposures are the result of production and use of formaldehyde and formaldehyde products.

✓ (2) Certain workplace levels (up to 1.5 ppm average) are typically one to two orders of magnitude above typical outdoor ambient levels.

✓ (3) Residential levels in homes using particleboard or urea-formaldehyde (U-F) foam insulation can have levels ~~as high as~~ of 0.03 ppm ~~to~~ with some exceeding over 2 ppm. These levels were measured in homes where the residents complained, so they ~~may not be~~ are probably biased to homes in which levels are elevated and may not be representative of all homes using particleboard or U-F foam.

(4) Typical ambient air levels in the U.S. range from about 0.001 ppm to about 0.030 ppm, considerably above a remote "background" reading of 0.0004 ppm.

comments seem to refer def.1.

Bauml conversions needed, [illegible]

This needs [illegible] the differences in analytical methods and [illegible] CA data as useful for [illegible] method used by CIIT

Table 4: Summary of Monitoring Results

| Description of study | Sampling & analytical methods[a] | Number of observations | Concentrations (ppm) min | mean | max | Comments |
|---|---|---|---|---|---|---|
| I. Occupational levels | | | | | | |
| A. Direct production of formaldehyde | | | | Kavg. mean | | |
| • Walk-through industrial hygiene study; 4-hour time-weighted averages; personal samplers NIOSH 1980b) | CT,IC | N.R.[b]<br>N.R.<br>N.R. | -<br>-<br>- | 1.60<br>1.12-<br>1.31<br>3⟌4.03<br>1.34 | -<br>-<br>- | formaldehyde operator<br>operator's assistant<br>laboratory technician |
| B. Users of formaldehyde and formaldehyde products | | | | | | |
| 1. Resin producers | | | | | | |
| • Walk-through industrial hygiene study; 4-hour time weighted averages; personal samplers (NIOSH 1980b) | CT,IC | N.R.<br>N.R. | -<br>- | 1.08 ~~1.11~~<br>1.71 | -<br>- | resin plant operator<br>operator's assistant |
| • Resin plant, M-F and P-F resins produced for paper binding (NIOSH 1976b) | BI,CT,OC | 8 | 0.05 ~~0.04~~ | 0.24 ~~0.22~~ | 0.38 ~~0.48~~ | breathing area on writing stands |
| a. Plywood and particleboard manufacture | | | | | | |
| • Manufacturing glue for plywood, samples over glue vat (NIOSH 1978b) | BI, CO | 2 | 0.09 ~~0.08~~ | - | 0.17 ~~0.12~~ | |
| • Plywood particleboard manufacture (NIOSH 1979a) | N.R. | N.R. | 1 | - | 2.5 | |
| I. Construction using plywood/particleboard | - | (no monitoring data available) | | | | |
| II. Occupational levels in particleboard/plywood containing offices | | | | | | |
| • Office trailers (Fanning 1979) | CA | 6 | 0.02 | 0.06 | 0.10 | |
| III. Particleboard veneering | | | | | | |
| • Particleboard veneering operation (Herrick et al. undated) | BI,CA | 11 ~~10~~<br>N.R.<br>9<br>~~14~~ 15 | 0.008<br>0.9<br>0.2<br>0.2 | 0.12 ~~[illegible]~~<br>2.75<br>0.4<br>~~0.55~~ 0.70 | 0.25 ~~30~~<br>6.4<br>0.55<br>~~2.5~~ 2.5 | plant<br>veneer press<br>veneer core press<br>core, veneer, adhesives |

check this? seems unreal

(Continued)

Table 4. (Continued)

| Description of study | Sampling & analytical methods[a] | Number of observations | Concentrations (ppm) min | mean | max | Comments |
|---|---|---|---|---|---|---|
| b. U-F foam manufacturers and distributors | | | | | | |
| • Two plants, air sample in work-rooms (Herrick et al. undated) | SS,IC | N.R. | 0.12 | - | 0.55 | resin production, plant C |
| | | N.R. | 1.8 | - | 5.4 | resin drumming, plant C |
| | | N.R. | 0.2 | - | 0.74 | drum washing, plant C |
| | | N.R. | 0.06 | - | 0.34 | foaming agent blending, plant C |
| | | N.R. | 0.34 | - | 0.45 | resin production, plant D |
| | | N.R. | 0.18 | - | 1.28 | resin drumming, plant D |
| • One plant (probably same data as plant C above), breathing zone samples (NIOSH 1980b) | BI,CA | 9 | 0.12 | 0.30 | .55 | cook |
| | | 9 | 0.17 | 1.5 | 5.4 | cook's assistant |
| | | 5 | 0.2 | 0.39 | 0.74 | drum washer |
| | | 5 | 0.06 | 0.19 | 0.34 | foaming agent blendor |
| I. U-F foam insulation dealers and installers | | | | | | |
| • Application of U-F foam insulation to commercial and residential buildings (Herrick et al. undated) | | N.R. | N.D.[c] | - | 1.5 ~~2.4~~ | applicator |
| | | N.R. | N.D. | - | 0.65 | laborer |
| | | N.R. | 0.07 | - | 2.0 | truck for transport of supplies & personnel |
| | | N.R. | 0.17 | - | 0.85 | warehouse |
| | | N.R. | N.D. | - | 0.5 | applicator s assistant |
| II. Occupational levels in U-F foam insulated buildings | | | | | | |
| • Suburban shopping center insulated with UF foam (NIOSH 1979a) | BI,CA | 36 | 0.8 | 1.05 | 1.6 | |
| | BI,IC | 30 | 0.3 | [illegible] ~~1.30~~ | 3.1 | |
| | DT | 16 | <0.5 | 1.56 | 3.0 | |
| c. Manufacturers of molded products | | | | | | |
| • Acetal resin (Celcon M9014) used in molding plastic sprayers and dispensers; breathing zones (NIOSH 1973a) | DT | N.R. | <2 | <2 | <2 | |
| • Celcon and Delvin polymers, breathing zones (NIOSH 1973c) | DT | N.R. | 0.01 | - | 4 | |
| | DT | 28 | <0.01 | - | 1.0 | |
| • Bronze foundry molds, UF resins (NIOSH 1976a) | BI,CA | ~~14~~ | ~~0.12~~ | ~~0.43~~ | ~~0.80~~ | 0.24 0.53 0.80 |
| | | 11 | | | | 0.12 0.39 0.69 |
| • Iron foundry (NIOSH 1979a) | N.R. | 14 | <0.02 | 0.43 | 18.3 | median instead of mean |

(Continued)

Table 4. (Continued)

| Description of study | Sampling & analytical methods[a] | Number of observations | Concentrations (ppm) min | mean | max | Comments |
|---|---|---|---|---|---|---|
| ~~c. Glass-molding using PF resins~~ | ~~BI,CT,CO~~ | ~~29~~ | ~~0.07~~ | ~~0.2~~ | ~~0.97~~ | ~~personal samples~~ |
| | | ~~29~~ | ~~N.D.~~ | ~~0.21~~ | ~~0.82~~ | ~~area samples~~ |
| • Iron casting, sand molding using paraformaldehyde-furfuryl alcohol (NIOSH 1973b) | BI,CA | 3 | 0.07 | ~~0.07~~ 0.16 | ~~0.35~~ 0.33 | personal samples |
| • Molding for products to measure temperature, PF resins (NIOSH 1977c) | BI,CO | 6 | 0.03 | 0.09 | 0.13 | personal samplers |
| | | 6 | 0.07 | 0.21 | 0.78 | stationary samplers |
| d. Textile manufacturers and storage (includes use of formaldehyde-based resins and formaldehyde itself.) | | | | | | |
| • Walk-through industrial hygiene survey, one permanent press facility (HEW 1966) | BI,I | 9 | 0.15 | 0.31 | 0.38 | workroom; note early date |
| • Eight permanent press facilities (HEW 1968) | BI,I | 5 | 0.3 | 0.85 | 1.7 | cutting (note early date) |
| | | 19 | 0 | 0.6 | 2.7 | sewing |
| | | 3 | 0.3 | 0.6 | 0.8 | pressing |
| | | 5 | 0.3 | 0.9 | 1.4 | storage |
| • Textiles warehouse (NIOSH 1979c) | CT,SP | 11 | 0.04 | 0.31 | 0.73 | workplace air |
| | BI,SP | 11 | 0.08 | 0.25 | 0.51 | |
| ~~• Permapress facility (NIOSH 1979d)~~ | ~~BI,SP~~ | ~~30~~ | ~~<0.1~~ | ~~[illegible]~~ 0.8 | ~~1.4~~ | |
| • Textiles facilities (NIOSH 1979e) | N.R. | 28 | 0.1 | 0.8 | 1.3 | plant A (median) |
| | | 15 | 0.1 | 0.7 | 1.4 | plant B (median) |
| e. Manufacturers of paper and paper products | | | | | | |
| • Paper treatment before bonding to form laminate. MF, PF resins used. Bonding also uses resins NIOSH 1976b) | BI,CT,CA | 15 | 0.04 | ~~0.07~~ 0.08 | ~~0.15~~ 0.16 | filter treating of paper-personal |
| | | 7 | 0.03 | ~~0.05~~ 0.06 | ~~0.07~~ 0.07 | filter treating of paper-area |
| | | 30 | 0.01 | 0.05 | ~~0.14~~ 0.23 | series B collating - personal |
| | | 10 | 0.02 | ~~0.03~~ 0.05 | ~~0.25~~ 0.28 | press buildup - personal |
| • Treated paper products, August 1978 (NIOSH 1979e) | N.R. | 64 | 0.14 | 0.59 | ~~0.90~~ 0.99 | median instead of mean |
| | | 37 | 0.14 | 0.34 | 0.90 | median instead of mean |
| f. Protective coating formulators & appliances | | (no monitoring data available) | | | | |
| g. P-F foam manufacturers, etc. | | (no monitoring data available) | | | | |

(Continued)

Table 4. (Continued)

| Description of study | Sampling & analytical methods[a] | Number of observations | Concentrations (ppm) min | mean | max | Comments |
|---|---|---|---|---|---|---|
| 2. Urea-formaldehyde concentrate producers | | (no monitoring data available) | | | | |
| a. Fertilizer manufacturers and appliers | | | | | | |
| • Fertilizer manufacture (NIOSH 1979a) | N.A. | 11 | 0.2 | 0.9 | 1.9 | area and personal samples |
| 3. Users of formaldehyde as a disinfectant and preservative | | | | | | |
| a. Producers of cosmetics and toiletries | | (no monitoring data available) | | | | |
| i. Cosmeticians, beauticians, etc. | | (no monitoring data available) | | | | |
| b. Embalmers and funeral services | | | | | | |
| • Cincinnati School of Mortuary Science (NIOSH 1980a) | CT | 3 | 0.51 | 2.1 | 3.99 | simulated worst case conditions |
| | | 5 | 1.3 | 2.7 | 3.93 | heavy workload, fan inoperative |
| | | 5 | 0.20 | 0.52 | 0.91 | normal workload, fan operative |
| c. Pathologists | | | | | | |
| • Hospital autopsy rooms (Covino 1979) | BI,CA | 10 | 0.06 | 4.8 | 7.9 | |
| • Autopsy room (NIOSH 1979a) | N.R. | 6 | 2.2 | 4.35 | 7.90 | median instead of mean |
| d. Biology instructors and students | | | | | | |
| • Biology lab (Schwartz 1980) | BI,CA | 8 | <0.1 | 8.3 | 14.8 | |
| e. Disinfectant Producers | | (no monitoring data available) | | | | |
| i. Sickroom/hospital applications | | (no monitoring data available) | | | | |
| ii. Drug production | | (no monitoring data available) | | | | |
| iii. Fermentation Industry Use | | (no monitoring data available) | | | | |
| iv. Dry cleaning | | (no monitoring data available) | | | | |
| v. Leather goods fumigant | | (no monitoring data available) | | | | |
| vi. Mushroom fumigant | | | | | | |
| • Mushroom farm, industrial hygiene survey (NIOSH 1980c) | DT | 12 | <0.5 | 2.68 | >10 | |
| | CT, IC | 3 | N.D. | ~~5.41~~ | ~~4.93~~ | - 2.70 |
| | | 3 | N.D | - | | 4.93 |

(Continued)

Table 4. (Continued)

| Description of study | Sampling & analytical methods$^a$ | Number of observations | Concentrations (ppm) | | | Comments |
|---|---|---|---|---|---|---|
| | | | min | mean | max | |
| f. Preservative production | | (no monitoring data available) | | | | |
| i. Wax, polish, adhesives users | | (no monitoring data available) | | | | |
| ii. Fats, oils users | | (no monitoring data available) | | | | |
| iii. Starch users | | (no monitoring data available) | | | | |
| iv. Users of photographic supplies | | (no monitoring data available) | | | | |
| v. Oil well drillers | | (no monitoring data available) | | | | |
| vi. Rubber industry workers | | (no monitoring data available) | | | | |
| • Rubber hose production (NIOSH 1977b) | BI,CO | ~~5~~<br>10 | ~~0.02~~<br>N.D | ~~0.03~~<br>0.04 | ~~0.04~~<br>0.033 | braid coating |
| 4. Deodorant manufacturers | | (no monitoring data available) | | | | |
| a. Spray deodorant use | | (no monitoring data available) | | | | |
| b. Glue processors | | (no monitoring data available) | | | | |
| c. Leather/skin processors | | (no monitoring data available) | | | | |
| d. Cork, tar, and mineral oil processors | | (no monitoring data available) | | | | |
| 5. Concrete and plaster producers | | (no monitoring data available) | | | | |
| a. Construction uses | | (no monitoring data available) | | | | |
| 6. Paper producers (also see under "Resins" above<br>• Bag manufacturer (NIOSH 1979b) | BI,CO | 101 | 0.14 | 0.44 | 0.99 | |
| 7. Organic chemical producers | | (no monitoring data available) | | | | |
| 8. Leather tanners | | (no monitoring data available) | | | | |
| 9. Asphalt shingle producers<br>• Asphalt shingle production (NIOSH 1978a) | BI,CO | 2 | 0.03 | 0.05 | 0.07 | |
| C. Occupational levels from indirect formaldehyde production | | | | | | |
| 1. Combustion engines<br>• Locomotive maintenance shop, diesel exhaust from engines receiving light maintenance (NIOSH 1973a) | N.R. | 15 | 0.015 | - | 0.07 | |

(Continued)

Table 4. (Continued)

| Description of study | Sampling & analytical methods[a] | Number of observations | Concentrations (ppm) min | mean | max | Comments |
|---|---|---|---|---|---|---|
| II. Consumer-related levels | | | | | | |
| A. Home residents (plywood/particleboard) | | | | | | |
| 1. Mobile homes | | | | | | |
| • State of Washington, 74 mobile homes containing particleboard (Wilson 1977) | CA | 226 ~~800~~ | <0.03 ~~<0.01~~ | 0.4 | 2.54 | |
| 2. Conventional homes | | | | | | |
| • Denmark, 25 rooms in 23 homes containing particleboard (Anderson, et al. 1975) | CA | 100 | 0.06 ~~0.08~~ | 0.50 ~~0.02~~ | 1.8 ~~2.24~~ | |
| • Four homes, one apartment building, one office with plywood/particleboard (Wilson 1977) | CA | 12 ~~N.R.~~ | 0.04 | - | 0.91 ~~[illegible]~~ | |
| B. Home residents (U-F foam insulation) | | | | | | |
| • Seven homes with people experiencing symptoms of exposure (Wilson 1977) | CA | 16 | 0.05 | 0.72 | 3.40 | |
| C. Home residents (both foam and particleboard) | | | | | | |
| • Wisconsin, 34 case files, (27 chipboard, 6 foam, 1 both, but data not resolvable into categories) (Woodbury and Zenz 1978) | BI,CA (?) | N.R. | 0.06 | - | 2.92 | 24 mobile homes, 10 conventional |
| • ~~Wisconsin, 10 homes (17 mobile) (Woodbury 1979)~~ | ~~CA (?)~~ | ~~116~~ | ~~0.02~~ | ~~0.88~~ | ~~4.15~~ | partly same data as above |
| • Washington, sampling due to complaints (Hallowell 1978) | N.R. | > 200 | 0.03 | - | 2.4 | mobile homes |
| • Minnesota, complaints (Garry et al. 1980) | N.R. | 275 | - | 0.65 | - | February |
| | | | - | 0.37 | - | March |
| | | | - | 0.22 | - | April |
| | | | - | 0.58 | - | May |
| | | | - | 0.99 | - | June |
| • Swedish homes, complaints (Suta 1980) | N.R. | 319 | 0.1 | 0.58 | 2 | |

(Continued)

Table 4. (Continued)

| Description of study | Sampling & analytical methods[a] | Number of observations | Concentrations (ppm) min | mean | max | Comments |
|---|---|---|---|---|---|---|
| D. Users of molded products | | (no monitoring data available) | | | | |
| E. Users of treated textiles | | (no monitoring data available) | | | | |
| F. Users of treated paper | | (no monitoring data available) | | | | |
| G. Users of fertilizers | | (no monitoring data available) | | | | |
| H. Users of pharmaceuticals | | (no monitoring data available) | | | | |
| I. Users of waxes, polishes, adhesives | | (no monitoring data available) | | | | |
| J. Users of fats, oils | | (no monitoring data available) | | | | |
| K. Users of starch | | (no monitoring data available) | | | | |
| L. Users of photographic supplies | | (no monitoring data available) | | | | |
| M. Users of rubber products | | (no monitoring data available) | | | | |
| N. Users of leather products | | (no monitoring data available) | | | | |
| ~~O. Smokers~~ | | | | | | |
| ~~● Inhaled cigarette smoke (Kensler and Battista 1963)~~ | ~~N.R.~~ | ~~N.R.~~ | ~~-~~ | ~~40~~ | ~~-~~ | |
| III. Ambient levels | | | | | | |
| A. Air | | | | | | |
| 1. Background | | | | | | |
| ● Enewetak Atoll, central equatorial Pacific Ocean (Zafiriou et al. 1980) | CO | N.R. | - | 0.0004 | - | ± 0.0002 |
| 2. U.S. ambient levels | | | | | | |
| ● Claremont, CA (L.A. Basin), Aug-Sep 1979 (Kok 1979) | CL | | 0.005 | 0.008 | 0.012 | typical summer day |
| | | new insert | - | 0.0308 | - | severe inversion |
| | | | - | 0.0178 | - | wildfire |
| ● Raleigh, NC, Fall 1972 | N.R. | N.R. | <0.03 | <0.03 | <0.03 | |
| Pasadena, CA, Summer 1973 | N.R. | N.R. | <0.03 | <0.03 | <0.03 | |
| Columbus, OH | N.R. | N.R. | - | 0.004 | - | |
| Iowa State Univ | N.R. | N.R. | - | 0.004 | - | |
| Maryland (Suta 1980) | N.R. | N.R. | - | 0.004 | - | |

(Continued)

Table 4. (Continued)

| Description of study | Sampling & analytical methods[a] | Number of observations | Concentrations (ppm) min | mean | max | Comments |
|---|---|---|---|---|---|---|
| • Pasadena, CA, Winter 1972, Summer 1973 (Hanst et al. 1976) | N.R. | N.R. | - | 0.000015 | - | |
| • Mission Viejo, CA | N.R. | N.R. | - | 0.014 | - | changed. |
| Ames, IA | N.R. | N.R. | <0.005 | <0.005 | <0.005 | |
| Long Beach, CA (Hollowell et al. 1979) | N.R. | N.R. | - | <0.03 | - | |
| • Claremont CA (Kok 1980a) | N.R. | N.R. | 0.005 | - | 0.030 | typical 0.01-0.02 |
| • Bayonne, NJ, May-Sept 1974 | CO | N.R. | - | 0.0061 | 0.020 | |
| Camden, NJ, May-Sept 1974 | | | - | 0.0038 | 0.014 | |
| Elizabeth, NJ, May-Sept 1974 | | | - | 0.0053 | 0.013 | |
| Newark, NJ, May-Sept 1974 (Cleveland et al. 1976) | | | - | 0.006 | 0.020 | |
| • Houston, TX, 1977 (Radian 1978) | CA,SP | N.R. | <0.005 | - | 0.012 | |
| • Houston, TX, Sept-Oct 1979 (Joshi 1979) | MB | 78 | 0.001 | 0.010 | 0.0276 | |
| B. Water | | | | | | |
| 1. Ambient water | | | | | | |
| • North Carolina, STORET data | CA | N.R. | <0.1 | <0.1 | <0.1 | |
| • Michigan, STORET data | CA | 4 | <0.1 | <0.1 | <0.1 | |
| 2. Rainwater | | | | | | |
| • Japan, acid rain (Saiki et al. 1977) | AA | 145 | 0 | 0.15 | 0.72 | |

[a] Abbreviations for analytical procedures:

| | |
|---|---|
| AA = Acetylacetone procedure | DT = Draeger tubes |
| BI = Bisulfite impingers | FS = Fourier transform spectrometer |
| CA = Chromotropic Acid procedure | GC = Gas chromatography |
| CL = Chemiluminescent procedure | IC = Ion chromatography |
| CO = Colorimetric analysis | MB = MBTH procedure |
| CT = Charcoal tubes | SP = Spectrophotometric procedure |
| SS = Solid sorbents | |

[b] N.R. = Not reported or not available

[c] N.D. = Not detected

technique for a one hour bubbler sample is reportedly 0.02 ppm. The UNC Carle method requires the injection of a 2 ml air sample into a column filled with Porapak Q. Light hydrocarbons pass directly through while formaldehyde, propylene, methanol, and acetaldehyde are retained. The precolumn is then placed in series with a second Porapak Q column and the contents passed into a high temperature methanizer before reaching the detector. The formaldehyde, as well as the carbonyl portion of the acetaldehyde molecule and methanol, is measured as methane by a flame ionization detector.

(5) Draeger Detectors

Color detector tubes, such as the Draeger detectors, are sealed glass tubes four to six inches long that contain reactive compounds. At sampling, the tubes are broken and a specified volume of air is passed through the tube. The formaldehyde in the air changes the indicator chemicals from white to pink. The extent of the color change is read through a calibrated numerical scale etched or printed on the tube so that the ppm in the air can be directly estimated. The range of detectability is 0.5 to 10 ppm with an accuracy of ±20 percent. This [illegible] other [illegible]

b. Formaldehyde in Water

There are two methods used for formaldehyde analysis in water, colorimetric and fluorometric.

(1) Colorimetric Method

Formaldehyde in water can be quantified by using a procedure involving phenylhydrazine hydrochloride and butyl alcohol.* Phenylhydrazine hydrochloride, potassium ferricyanide, and hydrochloric acid give a pink solution in the presence of formaldehyde. After development, the color is extracted by n-butyl alcohol and read spectrophotometrically at 520 nm. Results are not affected by the color or turbidity of the water sample although centrifugation may be necessary. The color follows Beer's Law to a lower limit of 0.7 ppm.

---

*Personal communication between Michael Keller, Versar, and Jane Edwards, North Carolina Department of Natural Resources and Community Development, Raleigh, NC, September 3, 1980.

## III. HEALTH EFFECTS ASSESSMENT

### A. Absorption and Metabolism

Formaldehyde can enter the body as a result of inhalation, ingestion, or dermal absorption. Absorption of formaldehyde through the upper respiratory tract in dogs has been estimated to exceed 95% of the inhaled dose (Egle 1972). Following oral exposure of dogs to formaldehyde, formate levels in the blood increased rapidly, indicating rapid uptake and metabolism (Malorny et al. 1965). Dermal absorption also has been demonstrated (Usdin and Arnold 1979), but does not appear to be significant in comparison to inhalation or ingestion.

Formaldehyde that enters the body appears to be converted rapidly to formate (Malorny et al. 1965; McMartin et al. 1979) or to combine with tissue constituents. The conversion of formaldehyde to formate occurs following intravenous (i.v.) infusion, subcutaneous injection, gastric intubation, or inhalation. Studies using i.v. infusion of 0.2M formaldehyde to dogs have shown that only a small amount of formaldehyde appears in the plasma during exposure (Malorny et al. 1965). This becomes undetectable within 1 hour after cessation of infusion. The peak formate concentration following formaldehyde infusion was the same as when formate (0.2M) itself was infused. The plasma half-life for formate (between 80 and 90 min.) was also similar. In the same study formaldehyde could not be detected after oral administration of 0.2M formaldehyde, although formate increased rapidly in the plasma with a half-life of 81.5 minutes.

Similar experiments using cynomolgus monkeys in which 0.2M formaldehyde was infused i.v., likewise, showed no accumulation of formaldehyde in blood (McMartin et al. 1979). The blood half-life was estimated to be 1.5 minutes. Similar half-lives for blood formaldehyde have been observed in rats, guinea pigs, rabbits, and cats (Rietbrock 1969). In a somewhat different experiment, McMartin et al. (1979) administered $C^{14}$-labeled methanol by gastric intubation. Again, formaldehyde could not be detected in the blood although formate levels increased rapidly. A study in which humans were exposed to formaldehyde gas (0.78 mg/m$^3$) for 3 hours also demonstrated a rapid rise in blood and urine formate levels (Einbrodt et al. 1976).

The rapid conversion of formaldehyde to formate occurred in many tissues in the various species examined, including human erythrocytes (Malorney et al. 1965), liver and brain; sheep liver; rat brain, kidney, and muscle; rabbit brain; and bovine brain and adrenals (Uotila and Koivusalo 1974). The enzymes involved have been studied by Strittmatter and Ball (1975) as well as by Uotila and Koivusalo (1974). The oxidative process is initiated by formation of S-formyl glutathione, which is then oxidized by NAD and finally cleaved by thiol esterase, releasing formic acid and glutathione. Formaldehyde also has been reported to be oxidized to formic acid by a nonspecific aldehydehydrogenase and through the tetrahydrofolic acid pathway (Huennekens and Osborn. 1959). Formaldehyde can also react with glycine to form serine, a reaction mediated by initial reaction with tetrahydrofolic acid (Blakely, 1955).

OK ✓

Additional studies (DuVigneaud et al. 1950) have shown that following subcutaneous administration of $^{14}$C-formaldehyde to rats, approximately 81% of the radioactivity appears as $CO_2$. A small amount of the radioactivity also was found in choline. Almost 60% of a subcutaneous dose of $^{14}$C-formate similarly appeared as $^{14}C$-$CO_2$, with small amounts of radioactivity in choline. Neely (1964) administered radiolabeled formaldehyde intraperitoneally (i.p.) to rats and found that 82% of the radiolabel was recovered as $CO_2$ and 13-14% as urinary methionine, serine, and a cysteine adduct. At lower doses, only radiolabeled methionine was formed. The author postulated that $CO_2$ was derived from serine (formed from glycine and $N^5$, $N^{10}$ methylene tetrahydrofolate) by deamination to pyruvate and oxidation in the Krebs cycle. The formation of methionine from $^{14}$C-formaldehyde and homocysteine had previously been demonstrated by Berg (1951). Formation of methionine would also account for the labeled choline observed by Duvigneaud et al. (1950) via methylation of phosphatidyl ethanolamine. More recent work by

(1975) have shown that mouse (C3Hf/A) and hamster (Syrian golden) lungs do not convert formate to $CO_2$ as efficiently as liver tissue does.

SEE ATTACHED INSERT

~~In summary, free formaldehyde is not usually found in plasma or other body tissues in measurable quantities; such endogenous formaldehyde as is produced may be reasonably presumed to be metabolized rapidly to formate or to enter the one carbon pool. When exogenous exposure does occur, formaldehyde is likewise rapidly metabolized to formate and excreted, converted to $CO_2$ and/or incorporated into other molecules.~~ The same paths seem to occur in all mammalian species examined to date, but reaction rates differ among various species and tissues. ~~Neither the ratio of metabolic deactivation to binding (to tissue or small molecules) nor the effect of route of exposure on this ratio is known at this time. Thus, although Egle's work (1972) suggests that the respiratory tract is the primary area at risk for tumor development, other body sites cannot be ruled out.~~

large

Tissue levels of 3-12 ppm are found (J.A. Heck, 1981)

thought

very

DELETE

too speculative

The overall metabolism of formaldehyde is summarized in Figure 8 (adopted from Kitchens et al. 1976 and Auerbach et al., 1977):

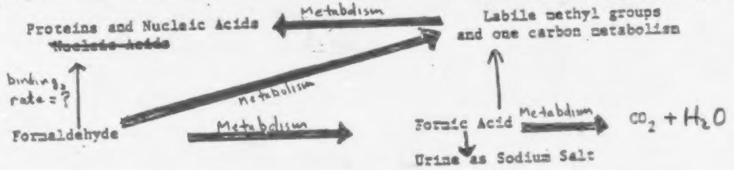
Proteins and Nucleic Acids
~~Nucleic Acids~~
Metabolism
Labile methyl groups and one carbon metabolism
binding, rate = ?
metabolism
Formaldehyde
Metabolism
Formic Acid
Metabolism
$CO_2 + H_2O$
Urine as Sodium Salt

Figure 8. Overall metabolism of formaldehyde (from Kitchens et al. 1976 ~~and Auerbach et al., 1977~~)

As can be seen from Figure 8, formaldehyde is more chemically active than any of its direct metabolites and would, therefore, appear to be the chemical substance of most concern for carcinogenicity. ~~A possibility exists, however, as proposed by Poverenny et al. (1975), that the actual carcinogenic agent may be an amino acid (or other) adduct.~~

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very speculative

Epi's Annotated Comments copy #1

generations (Della Porta et al. 1970). No evidence for transplacental carcinogenicity was found. It seems clear that, in contrast to long term repeated subcutaneous administration in rats, chronic ingestion of HMT was not carcinogenic to rats and mice. A study by Klenitzky (1940) in which "formol oil" was applied 50 times to the cervix uteri of mice (strain unknown) resulted in no tumors. It is difficult to interpret this experiment, however, because no information is available on the nature of the material used or on the quantities applied. These studies suggest that the route of exposure or nature of exposure is important to the toxic outcome of formaldehyde exposure.

## C. Epidemiology

Epidemiologic studies on the potential effects of formaldehyde exposure have focused on acute and chronic effects. The National Toxicology Program panel on formaldehyde was not aware of any published cohort or case-control studies specifically designed to study formaldehyde carcinogenicity. There are, however, several studies of cancer among individuals in occupations or industries involving formaldehyde and other chemicals. A discussion of these completed studies, and on-going and proposed epidemiologic studies which directly concern formaldehyde exposure and cancer are presented in Appendix A.

Findings of total excess cancers among workers in occupations and industries associated with formaldehyde and other chemicals, could raise a concern that formaldehyde may be a carcinogen. There does not appear, however, to be any particular type of cancer which was higher than expected. This lack of pattern, the lack of precise information concerning number of persons exposed to formaldehyde and the level of exposure, and problems of confounding exposures, make it difficult to interpret these reports. ~~[illegible]~~

~~[illegible]~~

The Proportionate Mortality Ratio (PMR) studies are also of limited value due to their lack of risk estimates. The National Cancer Institute (NCI) study among morticians ~~Moreover~~ is ~~an~~ ~~might~~ suggestive of ~~of~~ an association between formaldehyde and cancer (Walrath 1980). The Marsh (1980) study of Monsanto workers, showed however that among the population studied, no excess cancers occurred.

[illegible] suggestive of "death" study, which is confounded, [illegible] further [illegible] could [illegible] "might suggest" given [illegible] we have not [illegible] "might" [illegible] I don't [illegible]

~~to its limitations, this study does not provide definitive evidence that formaldehyde is not associated with cancer (Marsh 1980).~~ The NCI embalmers study results are ~~due in the summer of 1981~~ not yet available to us (Walrath 1980) and it is premature to judge the outcome of this study. ~~at this time~~

The cohort studies using the standard mortality ratio (SMR) analysis provide the best mechanism to determine whether formaldehyde is a human carcinogen. Six such studies are proposed or on-going; only one of these studies is complete. In this study, Wong (1980) found excess prostatic cancer among workers with a latency period of 20 years or more, and among workers with less than five years of employment; however, this finding may not be significant. The remaining SMR studies are due for completion starting the summer of 1981 through the winter of 1983. The latter date is for the NCI/Formaldehyde Institute study, which due to its size, provides the greatest chance of yielding definitive results. At present, the most prudent statement is that available ~~human~~ evidence does not ~~[illegible]~~ provide evidence of a significant hazard ~~but~~ ~~not~~ rule out ~~any or all risks~~ the site of risk in humans (Based on animal experiments) ~~would~~ may be the oral, nasal and pharyngeal tissues,

originally written

Note on editing? Although there may be more reason to expect respiratory (nasal, etc.) cancers, Wong's study indicates we shouldn't restrict examination to such sites.

do not type →

## IV. RISK ASSESSMENT

As discussed in the introductory section of this document, this assessment of formaldehyde is limited to evaluating the carcinogenic risk to man. Toxicologic effects other than carcinogenicity have not been addressed and no attempt has been made to determine effects on environmental biota.

The desired endpoint of a chemical risk assessment is the characterization of the effects of a chemical, identification of human populations and subpopulations that may come into contact with the compound, determinations of the amount of the chemical available to these populations, and the measurement or projection of the degree of risk that may be incurred by human contact with the chemical. These measurements then enable the quantification of the degree of risk and allow for establishing priorities among possible attempts to reduce or eliminate risk.

use revised I. Baumel calculations & better exposure vers.

nc O.K. they have been made available to Rich Daley.

Excerpts from Technical
Document of March 10, 1982

# TECHNICAL DOCUMENT: FORMALDEHYDE

DRAFT

March 10, 1982

## DISCLAIMER

This document is a preliminary draft which has not been released by the Office of Toxic Substances, Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency. It has not undergone scientific peer review and should not at this stage be construed to represent final Agency scientific or policy conclusions. It is being circulated for comments on its technical merit and policy implications.

Office of Toxic Substances
Office of Pesticides and Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

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through the 24-month sacrifice) exposed to 14.1 ppm formaldehyde. Three tumors also were detected at 24 months in rats exposed to 5.6 ppm formaldehyde although this incidence was not considered statistically significant by the CIIT investigators.

The CIIT bioassay protocol was reviewed by a panel of experts convened by the Consumer Product Safety Commission (CPSC), under the aegis of the National Toxicology Program (NTP), and found to be consistent with accepted standards for conducting inhalation exposure bioassays.

Because the available data indicate that formaldehyde is an animal carcinogen, and that its production and use may result in exposure of a number of segments of the population, the Agency has calculated the maximum likelihood estimates of risk for those populations. It should be noted, however, that because of limitations in the exposure data available to the Agency, and because the exposure level-response curve is highly non-linear, the projected risk estimates in Chapter IV may be overstated.

## I. BACKGROUND

The Chemical Industry Institute of Toxicology (CIIT) released preliminary information in October, 1979, which suggested that formaldehyde may induce cancer in rats following inhalation exposure. Information submitted to EPA under section 8(e) of the Toxic Substances Control Act (TSCA) by several formaldehyde producers stated that cancer had been found in three Fischer 344 rats in the CIIT study at the 15th month of a scheduled 24-month bioassay.

A later CIIT report released in January, 1980, revealed that by the scheduled 18-month sacrifice the number of nasal squamous cell carcinomas in formaldehyde-exposed animals had increased to a total of 36, as contrasted with no carcinomas in the control animals. Subsequently, the Consumer Product Safety Commission (CPSC), in conjunction with the National Toxicology Program (NTP), convened a panel of experts to review and evaluate the study protocol and preliminary results of the CIIT bioassay, as well as other available scientific literature on formaldehyde carcinogenicity. The panel report, issued November 21, 1980, concludes that "formaldehyde poses a cancer risk to humans". The degree of risk was not discussed.

The increased incidence of cancers among test animals in the 18-month sacrifice, the conclusion of the NTP panel report, and the widespread potential for exposure suggested that section 4(f) of TSCA may have been applicable to formaldehyde. The Office of Toxic Substances has developed this Technical Document to provide the Administrator with a technical basis on which to decide whether or not section 4(f) is applicable to formaldehyde at the present time. This document is restricted to: an evaluation of relevant carcinogenicity studies; identification of populations and subpopulations exposed to formaldehyde, including potential exposure levels; and providing preliminary estimates, where possible, of the carcinogenic risk to exposed populations.

and, hence, it is best used as a measure of total aldehydes. The sensitivity is given at 0.03 ppm formaldehyde/25 liters air sampled, assuming a minimum detectable absorbance of 0.05 absorbance units. At the recommended sampling rate of 0.5 l/min, this would yield a detectable concentration of 0.028 ppm for a one hour sample.

### (3) Pararosaniline Method

The pararosaniline method grew out of a wet chemical method for $SO_2$ which used a modified Shiff base (pararosaniline) and formaldehyde as color-development reagents (Kamens and Jeffries 1978). In the reverse procedure, a complex is formed when sodium tetrachloromercurate is added to sodium sulfite and formaldehyde. This complex (dichlorosulfitomercurate II) reacts with pararosaniline to yield a colored product that absorbs at 560 nm. Positive interferences from acetaldehyde and propionaldehyde have been observed in the 5 ppm region, although lower concentrations reportedly give no detectable response.

### (4) Gas Chromatographic Methods

Two gas chromatographic methods have been developed for the detection of formaldehyde: the Levaggi and UNC Carle methods (Kamens and Jeffries 1978). In the Levaggi technique, 4 μl of the liquid bisulfite collection solution is injected into a 12' x 1/8" analytical column. The sensitivity for this technique for a one hour bubbler sample is reportedly 0.02 ppm. The UNC Carle method requires the injection of a 2 ml air sample into a column filled with Porapak Q. Light hydrocarbons pass directly through while formaldehyde, propylene, methanol, and acetaldehyde are retained. The precolumn is then placed in series with a second Porapak Q column and the contents passed into a high temperature methanizer before reaching the detector. The formaldehyde, as well as the carbonyl portion of the acetaldehyde molecule and methanol, is measured as methane by a flame ionization detector.

### (5) Draeger Detectors

Color detector tubes, such as the Draeger detectors, are sealed glass tubes four to six inches long that contain reactive compounds. At sampling, the tubes are broken and a specified volume of air is passed through the tube. The formaldehyde in the air changes the indicator chemicals from white to pink. The extent of the color change is read through a calibrated numerical scale etched or printed on the tube so that the ppm in the air can be directly estimated. Because Draeger detectors are used as an indicator method, their range of detectability (0.5 to 10 ppm) and accuracy (±20 percent) are somewhat limited.

### b. Formaldehyde in Water

There are two methods used for formaldehyde analysis in water, colorimetric and fluorometric.

#### (1) Colorimetric Method

Formaldehyde in water can be quantified by using a procedure involving phenylhydrazine hydrochloride and butyl alcohol.* Phenylhydrazine hydrochloride, potassium ferricyanide, and hydrochloric acid give a pink solution in the presence of formaldehyde. After development, the color is extracted by n-butyl alcohol and read spectrophotometrically at 520 nm. Results are not affected by the color or turbidity of the water sample although centrifugation may be necessary. The color follows Beer's Law to a lower limit of 0.7 ppm.

#### (2) Fluorometric Method

Fluorometric analyses involve the reaction of formaldehyde with 2,4-pentanedione and ammonium acetate with heat to produce a solution of characteristic fluorescence (Afghan et al. 1974). The detection limit of this technique is approximately 10 ppb, and the coefficient of variation is 4.5. The fluorescent solution can absorb carbonyl compounds from the atmosphere, but more specific interferences were not reported.

### c. Formaldehyde in Food

Formaldehyde in food can be measured by extraction and gas chromatography/mass spectrometry or wet chemical techniques. In the wet

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*Personal communication between Michael Keller, Versar, and Jane Edwards, North Carolina Department of Natural Resources and Community Development, Raleigh, NC, September 8, 1980.

## III. HEALTH EFFECTS ASSESSMENT

### A. Absorption and Metabolism

Formaldehyde can enter the body as a result of inhalation, ingestion, or dermal absorption. Absorption of formaldehyde through the upper respiratory tract (locus not further defined) in dogs has been estimated to exceed 95% of the inhaled dose (Egle 1972). Following oral exposure of dogs to formaldehyde, formate levels in the blood increased rapidly, indicating rapid uptake and metabolism (Malorny et al. 1965). Dermal absorption also has been demonstrated (Usdin and Arnold 1979), but does not appear to be significant in comparison to inhalation or ingestion.

Formaldehyde that enters the body appears to be converted rapidly to formate (Malorny et al. 1965; McMartin et al. 1979) or to combine with tissue constituents. The conversion of formaldehyde to formate occurs following intravenous (i.v.) infusion, subcutaneous injection, gastric intubation, or inhalation. Studies using i.v. infusion of 0.2M formaldehyde (8 ml/min, total dose of 1.17 mMoles/kg) to dogs have shown that only a small amount of formaldehyde appears in the plasma during exposure (Malorny et al. 1965). This becomes undetectable within 1 hour after cessation of infusion. The peak formate concentration following formaldehyde infusion was the same as when formate (0.2M) itself was infused. The plasma half-life for formate (between 80 and 90 min.) was also similar. In the same study formaldehyde could not be detected after oral administration of 0.2M formaldehyde, although formate increased rapidly in the plasma with a half-life of 81.5 minutes.

Similar experiments using cynomolgus monkeys in which 0.2M formaldehyde was infused i.v., likewise, showed no accumulation of formaldehyde in blood (McMartin et al. 1979). The blood half-life was estimated to be 1.5 minutes. Similar half-lives for blood formaldehyde have been observed in rats, guinea pigs, rabbits, and cats (Rietbrock 1969). In a somewhat different experiment, McMartin et al. (1979) administered $C^{14}$-labeled methanol by gastric intubation. Again, formaldehyde could not be detected in the blood although formate levels increased rapidly. A study in which humans were exposed to formaldehyde gas (0.78 $mg/m^3$) for 3 hours also demonstrated a rapid rise in blood and urine formate levels (Einbrodt et al. 1976).

The rapid conversion of formaldehyde to formate occurred in many tissues in the various species examined, including human erythrocytes (Malorney et al. 1965), liver and brain; sheep liver; rat brain, kidney, and muscle; rabbit brain; and bovine brain and adrenals (Uotila and Koivusalo 1974). The enzymes involved have been studied by Strittmatter and Ball (1975) as well as by Uotila and Koivusalo (1974). The oxidative process is initiated by formation of S-formyl glutathione, which is then oxidized by NAD and finally cleaved by thiol esterase, releasing formic acid and glutathione. Formaldehyde also has been reported to be oxidized to formic acid by a nonspecific aldehydehydrogenase and through the tetrahydrofolic acid pathway (Huennekens and Osborn. 1959). Formaldehyde can also react with glycine to form serine, a reaction mediated by initial reaction with tetrahydrofolic acid (Blakely 1955).

Additional studies (DuVigneaud et al. 1950) have shown that following subcutaneous administration of $^{14}C$-formaldehyde to rats, approximately 81% of the radioactivity appears as $CO_2$. A small amount of the radioactivity also was found in choline. Almost 60% of a subcutaneous dose of $^{14}C$-formate similarly appeared as $^{14}C-CO_2$, with small amounts of radioactivity in choline. Neely (1964) administered radiolabeled formaldehyde intraperitoneally (i.p.) to rats and found that 82% of the radiolabel was recovered as $CO_2$ and 13-14% as urinary methionine, serine, and a cysteine adduct. At lower doses, only radiolabeled methionine was formed. The author postulated that $CO_2$ was derived from serine (formed from glycine and $N^5$, $N^{10}$ methylene tetrahydrofolate) by deamination to pyruvate and oxidation in the Krebs cycle. The formation of methionine from $^{14}C$-formaldehyde and homocysteine had previously been demonstrated by Berg (1951). Formation of methionine would also account for the labeled choline observed by Duvigneaud et al. (1950) via methylation of phosphatidyl ethanolamine. More recent work by Pruett et al. (1980) has demonstrated the incorporation of $^{14}C$-formaldehyde into the nucleic acid and protein fractions of WI 38 human diploid fibroblasts. Most of the radiolabel was found in RNA with lesser amounts in DNA and protein. The purine bases of both DNA and RNA were most heavily labeled. The radioactive incorporation identified in this study probably results from metabolism and not from direct chemical reaction. Small levels of direct binding, however, cannot be ruled out.

In addition to the serine pathway to $CO_2$ postulated above (Neely 1964), two other pathways have been identified, and are diagrammed in Figure 6.

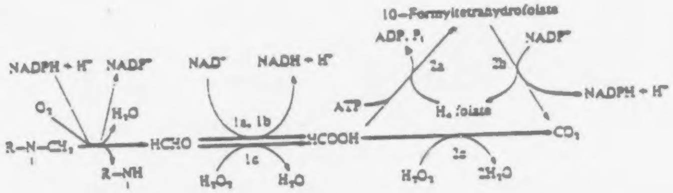
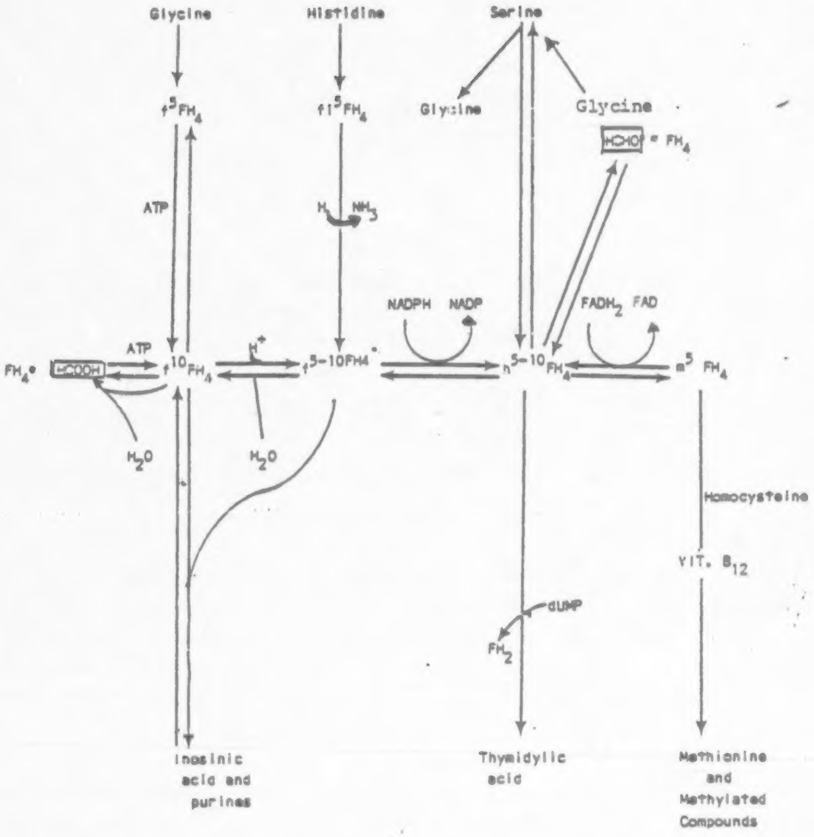


Figure 6. Simplified reaction sequence from drug N-demethylation (cytochrome-P-450-dependent monooxygenase) to formaldehyde, formate, and $CO_2$ production (from Waydhas et al. 1978). Reactions are: 1a, formaldehyde dehydrogenase (GSH); 1b, aldehyde dehydrogenase; 1c, catalase (peroxidatic mode); 2a, 10-formyltetrahydrofolate sythetase; 2b, 10-formyltetrahydrofolate dehydrogenase; 2c, catalase (peroxidatic mode).

Waydhas et al. (1978), McMartin et al. (1977), and Palese and Tephly (1975) have demonstrated that the catalase reaction (Figure 6) is not of major importance and that the primary pathway to $CO_2$ from formate occurs via the tetrahydrofolic acid


Glycine
Histidine
Serine
$f^5FH_4$
$fI^5FH_4$
Glycine
Glycine
HCHO = $FH_4$
ATP
H
$NH_3$
NADPH
NADP
$FADH_2$
FAD
$FH_4$ =
HCOOH
ATP
$f^{10}FH_4$
$H^+$
$f^{5-10}FH4$
$n^{5-10}FH_4$
$m^5$ $FH_4$
$H_2O$
$H_2O$
Homocysteine
VIT. $B_{12}$
dUMP
$FH_2$
Inosinic acid and purines
Thymidylic acid
Methionine and Methylated Compounds

$F4_4$ = Tetrahydrofolic acid
$f^{10}FH_4$ = $N^{10}$-formyltetrahydrofolic acid
$f^5FH_4$ = $N^5$-formyltetrahydrofolic acid
$f^{5-10}FH_4$=$N^5$,$N^{10}$-methenyltetrahydrofolic acid
$fI^5FH_4$ = $N^5$ -formiminotetrahydrofolic acid
$h^{5-10}FH_4$ = $N^5$,$N^{10}$ -methylenetetrahydrofolic acid

Figure 7. Tetrahydrofolic acid pathway and 1-carbon transfer for formaldehyde metabolism (from Kitchens et al. 1976).

pathway. This has been demonstrated in rat liver perfusates (Waydhas et al. 1978), monkeys (McMartin et al. 1977), and rats (Palese and Tephly 1975). Since the tetrahydrofolic acid pathway (Figure 7) can lead to the transfer of the carbon from formate to a number of other compounds (including serine), it is not clear that the 10-formyltetrahydrofolate dehydrogenase reaction (Figure 6) is the only reaction of importance for $CO_2$ production in this pathway.

The sources of formate in Figure 7 include the degradation of amino acids such as histidine and tryptophan, and possibly serine and glycine. Formation of formaldehyde or formate can also result from N-demethylation of drugs such as aminopyrine or ethylmorphine (Waydhas et al. 1978; Aebi and Roggen 1958) or the metabolism of dihalomethanes (Ahmed and Anders 1978).

Formaldehdye can be formed in mammalian tissues (pig brain and rat kidney) by enzymatic hydrolysis of 5-methyl tetrahydrofolate, in a reaction that appears to require the presence of biogenic amines. The reaction between the amine and formaldehyde is non-enzymatic and leads to the formation of various alkaloids (Laduron and Leysen 1975). A similar reaction involving $N^5,N^{10}$- methylene tetrahydrofolate is found in human lymphocytes, brain, kidney, and platelets (Thorndike and Beck 1977); it also apparently requires an amine acceptor. Formaldehyde can additionally result from the action of mixed function oxidases on the N-methyl groups of various xenobiotics (Gescher et al. 1979). These authors report, however, that the rate of oxidation of formaldehyde to formate is higher than the rate of formation of formaldehyde in the above reaction.

Finally, whereas the conversion of formaldehyde to $CO_2$ occurs in a similar manner in the different species studied, the relative importance of each reaction differs among species and tissues. Thus, the rat is able to convert formate to $CO_2$ at more than twice the rate of monkeys (or human) and, as a result, has lower blood formate levels (McMartin et al. 1977) and does not excrete formate in the urine (Neely 1964). Man additionally possesses 50% more hepatic dehydrogenase than do rats (Goodman and Tephly 1971). With regard to differences, Den Engelse et al. (1975) have shown that mouse (C3Hf/A) and hamster (Syrian golden) lungs do not convert formate to $CO_2$ as efficiently as liver tissue does.

In summary, free formaldehyde is not usually found in plasma or other body tissues in large quantities. It has been reported that enogenous formaldehyde was isolated from the nasal mucosa of unexposed rats at levels ranging from 6 ppm to 15 ppm; however, it is estimated that from 90% to 99% is bound (Heck, personal communication, 1981). Presumably, unbound formaldehyde can be metabolized very rapidly to formate or enter the one carbon pool.

The overall metabolism of formaldehyde is summarized in Figure 8 (adopted from Kitchens et al. 1976):

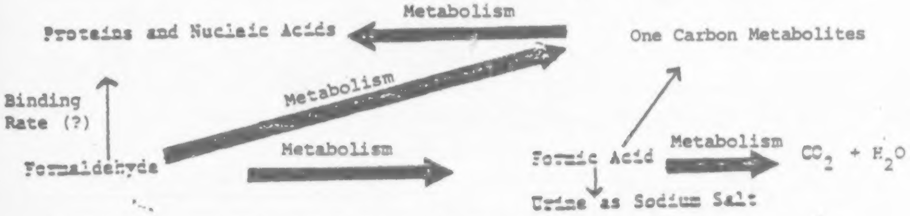

Metabolism
Proteins and Nucleic Acids
One Carbon Metabolites
Binding
Rate (?)
Metabolism
Formaldehyde
Metabolism
Formic Acid
Metabolism
$CO_2 + H_2O$
Urine as Sodium Salt

Figure 8. Overall metabolism of formaldehyde (from Kitchens et al. 1976).

As can be seen from Figure 8, formaldehyde is more chemically active than any of its metabolites and would, therefore, appear to be the chemical substance of most concern for carcinogenicity. The same paths appear to occur in all mammalian species examined to date.

## B. Carcinogenicity

A search of the scientific literature revealed only a few studies designed for the purpose of testing formaldehyde for carcinogenic activity. This section reviews only those studies which were conducted over a sufficient length of time (as determined by the CPSC/NTP Formaldehyde Panel 1980) to permit detection of any carcinogenic action of the test chemical.

By far the most important and best designed carcinogenesis study conducted to date with formaldehyde is the CIIT inhalation study recently reported by Swenberg et al. (1980). Fischer 344 rats and B6C3F$_1$ mice (120 male and 120 female rats or mice per group) were chronically exposed to 2.1, 5.6, and 14.1 ppm of formaldehyde vapors for 6 hrs. per day, 5 days per week. During the first 18 months of exposure, 2, 2, 8 and 44 rats died in the groups exposed to 0, 2.1, 5.6, and 14.1 ppm of formaldehyde, respectively. Of the 44 rats which died spontaneously in the group exposed to 14.1 ppm, 32 had nasal tumors (28 squamous carcinomas and 4 squamous papillomas). Many of the rats also showed hyperplastic and metaplastic lesions of the nasal epithelium. Hyperplastic and metaplastic lesions also were detected in rats exposed to 5.6 ppm formaldehyde (14 lesions were found in 8 rats), indicating that the nasal epithelium was significantly damaged at this lower level of exposure. At 18 months of exposure, 40 rats were killed in each group. Eight of 40 rats exposed to 14.1 ppm had developed nasal squamous carcinomas. Although no carcinomas of the airways were found in the other groups, one adenomatous polyp was found in one rat of each of the groups exposed to 2.1, 5.6 and 14.1 ppm. In addition, a large number of hyperplastic and metaplastic lesions was detected in the nasal epithelium of these rats, even at formaldehyde concentrations as low as 2.1 ppm.

Although the final histopathology is not complete, preliminary results of the terminal sacrifice, carried out in early June 1980, were reported at the Chemical Industry Institute of Toxicology's Conference on Formaldehyde Toxicity in November

1980.* At that time, Drs. Swenberg and Kerns indicated that the number of tumors in the rats exposed to 14.1 ppm had risen to 95. Additionally, three tumors were found in rats exposed to 5.6 ppm and in two mice exposed to 14.1 ppm.

One complication noticed during the CIIT study was a spontaneous outbreak in rats of sialodacryoadenitis. The evidence for this consisted of (a) decreased body weight in all dosed and control rat groups at about the 52nd week of the experiment, followed by prompt recovery of body weight; and b) histopathologic demonstration of typical lesions in lacrimal and salivary glands and in the upper respiratory tissues of dosed and control rats in the 12-month sacrifice groups. Evidence of sialodacryoadenitis was not found in rats sacrificed at 6 or 18 months or in those with unscheduled deaths. Virus isolation, viral antigen demonstration, and serologic tests for antibodies were not attempted in rats or mice.

With regard to formaldehyde in the exposure chamber, a panel of experts reviewed the method of formaldehyde generation and monitoring and agreed that "the Battelle approach to formaldehyde vapor generation was a suitable adaptation of accepted methods and principles and, therefore, was sound and based upon the best available technology. The same type of assessment applied to the chamber air monitoring system, which also combined two well-established procedures" (Gralla et al. 1980).

The results of the CIIT bioassay, thus, are sufficient to establish that formaldehyde is an animal carcinogen. Based on the differences in response to exposure shown by rats and mice, different species may have differing sensitivities but this is a quantitative rather than a qualitative difference. It can be expected that under certain conditions of exposure that formaldehyde gas could pose a carcinogenic risk to humans.

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*Personal communication from Drs. J. Swenberg, Chemical Industry Institute of Toxicology and W. Kerns Battelle Columbus Laboratories, to R. Dailey, Office of Toxic Substances, U.S. Environmental Protection Agency, November 20, 1980.

Suggestive evidence for the carcinogenicity of inhaled formaldehyde vapors also comes from a study by Albert et al. (1980). One hundred male Sprague Dawley rats were exposed to a mixture of gaseous formaldehyde (14.7 ppm) and hydrogen chloride (10.6 ppm) for 6 hours/day, 5 days/week for life. Twenty-seven percent of the exposed rats developed nasal tumors of which 25 were squamous carcinomas and 2 were papillomas. No nasal tumors were found in 100 control rats. Both dosed and control rats had pneumonia but the lesions were more severe in dosed rats. The estimated bis(chloromethyl)ether (BCME) level in the exposure chamber (developing as a result of the chemical interaction of formaldehyde and hydrogen chloride) was 1 ppb. This value was computed on the basis of 10 measurements made in the mixing chamber during the course of the study. It is not certain whether the high nasal cancer incidence was a result of the formaldehyde exposure, the (presumed) BCME exposure, or the biological interaction of the two or three components of the gas mixture. Based on their previous studies (Kuschner et al. 1975), the authors considered the BCME level to be too low to be a significant etiological factor for the nasal cancers observed in this study. They also point to the fact that in rats, BCME causes mostly esthesioneuroepitheliomas rather than squamous carcinomas in the nasal cavities. While the results suggest that formaldehdye (rather than BCME) is the major etiological agent in this experiment, considerable uncertainty remains, and other interpretations are possible. The authors' comparison of 20 exposure days at 100 ppb of BCME (Kuschner et al. 1975) with 500 exposure days at 1 ppb of BCME (Laskin et al. 1980) does not, however, resolve the uncertainty of comparing the different factors involved in dose-rate versus total delivered dose in tumor induction.

Three other chronic inhalation studies with formaldehyde designed to investigate possible cocarcinogenic effects of this agent in the upper and lower airways have been reported (Nettesheim 1977, Horton 1963, Dalbey and Nettisheim 1980). Since the nasal tissues were not systematically examined histologically, the value of these studies in assessing the carcinogenicity of formaldehyde is accordingly limited. In spite of these reservations, the studies have some bearing on the problem of formaldehyde carcinogenicity. In the studies conducted at the Oak Ridge National Laboratory (ORNL) by Nettesheim and colleagues (Nettesheim 1977), Syrian golden hamsters were exposed by intratracheal (i.tr.) instillation to different doses of benz(a) pyrene (BaP) and by inhalation to various concentrations of formaldehyde (acrolein exposures were carried out in parallel studies). Two types of formaldehyde exposure schedules were used: 10 ppm for 5 hrs/day, 5 days/week for life (2 groups) and 20 or 50 ppm for 5 hrs/day, 1 day/week for 17 weeks (7 groups). In all, 9 groups of 88 hamsters each were exposed to formaldehyde (with or without BaP exposures; 2 groups were exposed to formaldehyde only). Significant in the context of this discussion is that no macroscopically recognizable nasal tumors were observed in hamsters, whereas, in the studies with rats by Swenberg et al. (1980), and by Albert et al. (1980) grossly visible tumors developed. Based on extensive histopathological evaluation, there was no evidence for the carcinogenicity or cocarcinogenicity of formaldehyde for the larynx, trachea and lower airways. Although the level of sectioning was not rigorously controlled, no neoplasms were found in two sections of nose from each hamster. This suggests that there may be significant variation in susceptability among species.

In the study reported by Horton et al. (1963), C3H mice were exposed to coal tar aerosol and/or to formaldehdye at concentrations of 40, 80, and 160 ppm. Exposures were carried out for 1 hr/day, 3 days/week for 35 weeks, except for the 160 ppm group which was exposed only for 4 weeks because of toxicity. Only 15 mice survived to 1 year. There is no mention of histopathological evaluation of nasal tissues, so presumably no grossly visible tumors were observed. Coal tar aerosol exposure resulted in lung tumor formation in 5 animals (1 invasive carcinoma) but formaldehyde exposure did not. No evidence was found for any cocarcinogenic effects of formaldehdye. The major shortcomings of this study for evaluating the carcinogenic activity of formaldehyde are that too few animals survived past one year, the individual exposures were short, most groups were exposed only for 35 weeks, and histopathology was inadequately reported. The failure to observe lung tumors in this and other studies is significant to limiting the site of action of inspired formaldehyde to the nasal tissues. This agrees with the work of d'A. Heck (CIIT 1980) on formaldehyde uptake and distribution.

A third study (as yet unpublished) has been performed by Dalbey and Nettesheim at the Oak Ridge National Laboratory (1980). In this study, male Syrian Golden hamsters were exposed to diethylnitrosamine (DEN) subcutaneously (0.5 mg once weekly for 10 wks.) and to inhalation of either nitrogen dioxide (10 ppm) or formaldehyde (30 ppm). Exposures to $NO_2$ and formaldehyde were made once weekly for 48 hours prior to each DEN injection and were subsequently continued for a lifetime after DEN injections were completed. An analysis of tumor data indicate that formaldehyde (but not nitrogen dioxide) might act as a tumor "enhancing agent" in the trachea, as measured by multiplicy of tumors. A major limitation in evaluating the carcinogenicity of formaldehyde from this study is that at the doses used, DEN alone produced tumors in a high proportion of animals.

The carcinogenicity of formaldehyde also has been tested by a variety of other routes of administration including subcutaneous injection in rats (Watanabe et al. 1954, 1955), ingestion by mice and rats (Della Porta et al. 1968, 1970), uterine cervical application in mice (Klenitzky 1940), and application to the buccal mucosa in rabbits (Meuller et al. 1978). Because of shortcomings in experimental protocols, none of these studies permits firm conclusions regarding formaldehyde carcinogenicity. Nonetheless, some of the studies give definite clues that formaldehyde may be carcinogenic to a variety of target tissues as well as a variety of animal species (and not only to the nasal epithelium of rats).

The most revealing study in this regard is that by Meuller et al. (1978) who applied a solution of 3% formalin to the oral mucosa of rabbits, using an "oral tank." Each exposure lasted for 90 minutes and was repeated 5 times per week for a period of 10 months. As a result, 2 out of 6 rabbits developed grossly visible leukoplakias that, according to the authors, showed histological features of carcinoma in situ. Unfortunately, the information given on the histomorphology of the lesions is very scanty. Nevertheless, the reported observations appear to be consistent with the rat inhalation studies, suggesting that formaldehyde is a carcinogen.

Also of potential significance are the observations reported by Brusick et al. (1980) concerning the transformation of mouse Balb 3T3 cells in vitro by formaldehyde concentrations as low as 0.5 ug per ml of culture fluid. At this time, no other pertinent information is available on these studies.

Probably the earliest experiments which suggest that formaldehyde is a carcinogen are those by Watanabe et al. (1954, 1955), who injected rats (strain unknown) subcutaneously with 0.4% formalin at a dose of 1 ml per week for 15 months (Watanabe et al. 1954) and with 9-40% of hexamethylene-tetramine (HMT, from which formaldehyde is liberated in vivo), 1-2 ml per week, until tumor development (Watanabe and Sugimoto 1955). In the first study (Watanabe et al. 1954) 4 out of 10 rats developed sarcomas at the site of the injection and in the second study (Watanabe and Sugimoto, 1955), 8 out of 20 rats developed tumors, 7 sarcomas and 1 adenoma. There is little doubt that tumors were induced by the subcutaneous injections of both chemicals over many months. It is not certain, however, what the role of the repeated severe injury to the subcutaneous tissue may have been in the induction of the sarcomas, even through results with formic acid were negative (Watanabe and Sugimoto 1955).

Several other studies carried out with HMT resulted in negative findings. Brendel (1964) administered HMT daily by gavage to 15 male and 15 female BD rats (0.4 gm per day) for 333 days. No treatment related tumors were observed. Della Porta et al. (1968) administered HMT in the drinking water to CTM, SWR and C3Hf mice (1.25-12.5 g/kg body weight/day for up to 60 weeks) and to Wistar rats (1.5-2.5 g/kg body weight/day for 104 weeks). No treatment-related tumors were observed. Negative test results were also reported in a subsequent study in which Wistar rats were given 2% HMT in the drinking water over three consecutive generations (Della Porta et al. 1970). No evidence for transplacental carcinogenicity was found. It seems clear that, in contrast to long term repeated subcutaneous administration in rats, chronic ingestion of HMT was not carcinogenic to rats and mice. A study by Klenitzky (1940) in which "formol oil" was applied 50 times to the cervix uteri of mice (strain unknown) resulted in no tumors. It is difficult to interpret this experiment, however, because no information is available on the nature of the material used or on the quantities applied. These studies suggest that the route of exposure or nature of exposure is important to the toxic outcome of formaldehyde exposure.

## C. Epidemiology

Epidemiologic studies on the potential effects of formaldehyde exposure have focused on acute and chronic effects. The National Toxicology Program panel on formaldehyde was not aware of any published cohort or case-control studies specifically designed to study formaldehyde carcinogenicity. There are, however, several studies of cancer among individuals in occupations or industries involving formaldehyde and other chemicals. A discussion of these completed studies, and on-going and proposed epidemiologic studies which directly concern formaldehyde exposure and cancer are presented in Appendix A.

Findings of excess total cancers among workers in occupations and industries associated with formaldehyde and other chemicals, could raise a concern that formaldehyde may be a carcinogen. There does not appear, however, to be any particular type of cancer which was higher than expected. This lack of pattern, the lack of precise information concerning number of persons exposed to formaldehyde and the level of exposure, and problems of confounding exposures, make it difficult to interpret these reports.

The Proportionate Mortality Ratio (PMR) studies are also of limited value due to their lack of risk estimates. The National Cancer Institute (NCI) study among morticians might suggest an association between formaldehyde and cancer (Walrath 1980). The Marsh (1980) study of Monsanto workers, however, showed that among the population studied, no excess cancers occurred. The NCI embalmers study results are not yet available to us (Walrath 1980) and it is premature to judge the outcome of this study.

# APPENDIX 4

## ATTACHMENTS

1. FORMALDEHYDE IN INDOOR AIR TOXICITY AND RISK, A. G. Ulsamer, K. C. Gupta, M.S. Cohn, and P. W. Preuss Consumer Product Safety Commission, Bethesda, Md. 20207

2. Selikoff, I. J., and Hammon, E. C. Carcinogenicity of Formaldehyde, Report to the American Cancer Society by the Environmental Cancer Information Unit, Feb. 25, 1981.

3. IARC Formaldehyde Working Group Meeting Oct. 1981, 3rd Draft No. 18, IARC/WP 81c.

4. Report of the Federal Panel on Formaldehyde Environmental Health Perspectives, Vol. 43, pp. 139-168, 1982.

5. NIOSH Current Intelligence Bulletin 43, April 15, 1981.

6. CPSC Memorandum dated February 19, 1982, Subject: Health Sciences Analysis of Comments on the Proposed Ban of UFFI.

FORMALDEHYDE IN INDOOR AIR: TOXICITY AND RISK, A.G. Ulsamer, K.C. Gupta, M.S. Cohn, and P.W. Preuss, Consumer Product Safety Commission, Bethesda, MD 20207.

Formaldehyde is a highly reactive gas with a pungent odor. It is released from a va of sources including urea-formaldehyde foam insulation (UFFI), particle board, plywo and various combustion processes. Concentrations of formaldehyde associated with th presence of these products are higher indoors than outdoors. Under controlled condit formaldehyde causes eye and nasal irritation at air concentrations of 0.2 and above. Exposure in homes, or occupationally, has been associated with eye, nose and throat irritation, coughing, wheezing, skin rashes, nausea, and other symptoms; formaldehyde also a sensitizer. Individuals who are allergic to formaldehyde, or who suffer from respiratory diseases, are likely to suffer the effects of formaldehyde at even lower concentrations. Recent studies have indicated that formaldehyde is also a carcinogen in rats and probably in mice. Based on its known metabolism, reactivity with DNA and other macromolecules as well as its mutagenic effects in many test systems, formaldeh is thought to be genotoxic. Epidemiological studies to date have been inadequate to determine whether or not formaldehyde is a human carcinogen. Since formaldehyde is a direct acting carcinogen, it is likely to pose a carcinogenic risk to humans. This ri may be estimated by means of the multistage cancer model to be up to 51/million for individuals exposed to UFFI for 9 years.

# FORMALDEHYDE IN INDOOR AIR: TOXICITY AND RISK

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The Consumer Product Safety Commission (CPSC) has received over 3,000 complaints to date involving consumer exposure to formaldehyde vapor released from building materials. Of these about 2,000 involve urea-formaldehyde foam insulation (UFFI). Most of the remainder involve plywood, particle board, paneling, and other wood products in mobile homes; a few are due to other sources of formaldehyde. These include: a) furnishings; b) fueled appliances; c) other consumer products; and d) human activities.

The release of formaldehyde from such sources causes formaldehyde levels indoors to be higher than outdoor levels. Ambient (outdoor) levels of formaldehyde generally average less than 0.03 ppm even in urban areas (NAS, 1981). Indoor levels of formaldehyde may range from less than 0.01 to approximately 3 ppm. Data compiled by the Directorate of Health Sciences on formaldehyde levels in homes are summarized in Table I.

Table I
FORMALDEHYDE CONCENTRATION IN HOMES

| | Type of Home | n | Formaldehyde Concentration (ppm) Range | Average |
|---|---|---|---|---|
| 1. | Homes without UFFI | 41 | 0.01-0.08 | 0.03 |
| 2. | Homes with UFFI | 636 | 0.01-3.4 | 0.12 |
| 3. | Mobile Homes | 431 | 0.01-2.93 | 0.38 |
| 4. | Ambient | 156 | 0.0-0.08 | 0.01 |

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1. The opinions expressed in this article are those of the authors and do not necessarily represent the views of the Commission. This article was written by the authors in their official capacity and thus is in the public domain and may be freely copied or reprinted.

Homes insulated with urea-formaldehyde foam (UFFI) have significantly higher formaldehyde concentrations ($p < 0.02$) than non-UFFI homes. On the basis of data collected on UFFI installed in panels under near ideal conditions, it has been estimated that UFFI at 25°C can contribute 0.05 to 0.4 ppm to the formaldehyde level of the home. When similar UFFI panels were tested at 23°C, 33°C, and 40°C, (temperatures which may be encountered in wall cavities) the average concentration of formaldehyde emitted from the panels increased six-fold at 33°C and thirteen-fold at 40°C, compared to those at 23°C.

Human Effects

The effects of formaldehyde on human health derive in part from its properties as a strong irritant and sensitizer. Exposure to formaldehyde can produce a variety of symptoms depending on the mode, duration, and concentration of exposure. Low level exposure to formaldehyde in healthy adults produced statistically significant irritant responses of the eye, nose, and throat at 0.2 ppm and above under controlled experimental conditions (Anderson, 1979; Rader, 1974; Weber-Tschopp et al., 1977). The severity of these responses, as well as the percentage of subjects that responded, increased in a dose-related manner. The lowest effective concentration of formaldehyde and the observed effects in controlled human and animal studies are summarized in Table II (attached). On the basis of available animal and human studies, the National Academy of Sciences concluded that there is no population threshold for the irritant effects of formaldehyde (NAS, 1980).

Repeated exposure in residential and occupational settings has been reported to result in prolonged eye, nose, and throat irritation, coughing, wheezing, diarrhea, nausea, vomiting, headaches, dizziness, lethargy, irritability, disturbed sleep, olfactory fatigue, and skin irritation among others. These studies are summarized in Table III (attached).

Formaldehyde exposure in homes (mobile homes or UFFI homes) at concentrations ranging from 0.01 to 3.4 ppm produced a variety of adverse health effects (Breysse, 1977; Sardinas et al., 1979; Garry et al., 1980). In mobile homes, where the formaldehyde concentrations were below 1.7 ppm in all but 2 of the over 80 measurements taken, eye, nose, and throat irritation, cough, wheezing, diarrhea, nausea and vomiting, headaches and skin rashes were reported (Garry et al., 1980). The authors stated that persons with a history of asthma tended to report adverse effects from exposure at lower levels. In another mobile home study, where 90% of the measured formaldehyde concentrations were below 1 ppm, the symptoms experienced included drowsiness, nausea, and headaches, as well as irritation of the eye, nose, and respiratory tract (Breysse, 1977). Some cases of severe formaldehyde sensitization were also reported. In UFFI homes, where formaldehyde concentrations ranged between 0.01 ppm and 3.4 ppm, the reported symptoms were eye irritation, respiratory symptoms, nausea, headaches, dizziness, and fatigue (Sardinas et al., 1979). In a recent study (Thun et al., 1980) comparing newly acquired symptoms among persons living in UFFI homes and non-UFFI homes, the evidence indicated that there were acute health effects due to UFFI. Both "skin burning" and "wheezing or difficult breathing" were present in a statistically significant excess and were correlated with households reporting persistent odor. Formaldehyde concentrations were not measured in these homes.

Occupational exposure to formaldehyde from various sources has generally caused eye, nose, and throat irritation (lacrimation, sneezing, coughing, dry and sore throat), as well as skin irritation (Yefremov, 1970; Gamble et al., 1976; Schoenberg and Mitchell, 1975; Kerfoot and Mooney, 1975). Other reported symptoms included headaches, dizziness, thirst, lethargy, irritability, disturbed sleep, inability to concentrate, moodiness, paranoia, crying without a cause, and a crawling sensation of the skin (Kamchatnov and Gayazova, 1971; Morrill, 1961; Ahmad and Whitson, 1973; Helwig, 1977). In addition, asthmatic reactions have been reported from exposure to formaldehyde (Paliard et al., 1949; Nova and Touraine, 1957; Sakula, 1975; Hendrick and Lane, 1977). Continued exposure for long periods can also lead to changes of the respiratory tract, such as chronic rhinitis and chronic pharyngitis (Yefremov, 1970).

In women exposed to formaldehyde, alterations in reproductive function were noted. These changes included a high incidence of menstrual disorders, pregnancy complications, and low birth weight of children (Shumilina, 1975). Secondary amenorrhea indicating depressed ovarian function and characterized by reduced levels of urinary steroids which were inversely proportional to the duration of employment was also reported (Kolesnikova, 1974).

Dermal exposure to formaldehyde may cause an acute inflammatory reaction of the affected region (Pirila and Kilpio, 1949; Roth, 1969) and/or allergic dermatitis. Acute allergic (eczematous) dermatitis is characterized by erythema, edema, papules, vesiculation, and oozing. Vesiculation is less prominent in chronic lesions which are characterized by lichenification, fissuring, and scaling. The lowest formaldehyde concentration that produced a dermal sensitization response under controlled conditions in a sensitized individual is 0.2 ppm in water (Horsfall, 1934). In a recent controlled study, Jordan et al., (1979) noted that persons sensitized to formaldehyde responded in patch tests to aqueous formaldehyde concentrations as low as 30 ppm. The authors concluded that most sensitized individuals would be able to tolerate dermal exposure to products containing up to 30 ppm of formaldehyde.

Repeated exposure to formaldehyde liquid (and probably even formaldehyde gas) can cause certain individuals to become sensitized. Similarly, repeated inhalation or dermal contact with formaldehyde has induced sensitization in rats and guinea pigs (Ostapovich, 1975; Maurer et al., 1975; Scheper et al., 1976; Maibach, 1978). When exposed to formaldehyde, sensitized individuals may exhibit allergic dermatitis (Horsfall, 1934; Pirila and Kilpio, 1949; Hovding, 1969), or mild to severe asthmatic reactions (Paliard et al., 1949; Nova and Touraine, 1957; Sakula, 1975; Hendrick and Lane, 1977). Asthmatic reactions may also occur by an irritative mechanism in individuals with hyperreactive airways (NAS, 1981). The National Academy of Sciences has estimated that 10-12% of the United States population may have hyperreactive airways which may make them more susceptible to the irritant effects of formaldehyde (NAS, 1981). Predictive tests conducted on normal subjects with 0.037% to 3.7% formaldehyde at induction followed by 0.37% formaldehyde at challenge, showed that 4.5 to 7.8% of the test population became sensitized (Marzulli and Maibach, 1974).

## Teratogenic Effects

Studies conducted in dogs and rats to examine the teratogenic potential of formaldehyde have been basically negative. Only a slight increase in the percentage of still-born pups and a slight decrease in weight gain (Hurni and Ohder, 1973), and some histological changes of the lymphoid tissue and liver (Gofmekler and Bonashevskaya, 1969) have been noted. Gross malformations were not observed (Gofmekler and Bonashevskaya, 1969; Della Porta et al., 1970; Natvig et al., 1971; Hurni and Ohder, 1973; Marks et al., 1980). Other effects in animals are shown in Table II.

## Genetic Effects

Formaldehyde has been demonstrated to be mutagenic in bacteria, fungi, insects, and mouse lymphoma cells (Auerbach et al., 1977; Gupta et al., 1982). Formaldehyde also induced chromosomal breaks and recombination in yeast, insects, and cultured mammalian cells as well as in intact animals (rats) (Auerbach et al., 1977; Gupta et al., 1982). In addition, formaldehyde induced base pair substitution in Ames tests (Griesemer et al., 1980, Gupta et al., 1982) and cellular transformation in Balb/c 3T3 cells (Brusick, 1980).

## Carcinogenic Effect

Of additional concern is the carcinogenic potential of formaldehyde in humans. This concern is based on metabolism, mutagenicity, and carcinogenicity studies which were reviewed in the Report of the Federal Panel on Formaldehyde (Griesemer et al., 1980). In brief, the panel reported that these studies showed that formaldehyde reacts readily with biological chemicals, including proteins and nucleic acids. Formaldehyde may also be converted to formate and excreted in the urine, or to carbon dioxide and exhaled. Formaldehyde can also enter the carbon pathway via reaction with tetrahydrofolic acid and be incorporated into lipids, nucleic acids and amino acids. These reactions are similar in laboratory animals and man, although the reaction rates may vary. Free formaldehyde has not been demonstrated in animals to date (Gibson, 1981).

Earlier studies to determine the carcinogenic potential of formaldehyde have involved: a) inhalation exposure in mice (Horton, 1963) and hamsters (Nettesheim, 1975, 1976 and 1977), b) intravaginal placement of "formol oil" (formaldehyde in vegetable oil) in mice (Klenitzky, 1940) and c) oral ingestion of hexamethylenetetramine (which breaks down to ammonia and formaldehyde in the stomach and kidneys) in rats and mice (Brendel, 1964; Della Porta et al., 1968, 1970; Natvig et al., 1971). The interpretation of the results of these studies, all of which were negative, is complicated by a variety of shortcomings relating to the extent of histopathology, dose, duration, number of animals tested, and route of administration, as well as the chemical form tested. When tested as a co-carcinogen in hamsters with benzo(a)pyrene (Nettesheim, 1975, 1976, 1977) or diethylnitrosamine (Dalbey and Nettesheim, 1980), formaldehyde did not increase the percentage of diethylnitrosamine or benzo(a)pyrene-induced tumor-bearing animals, but did increase the number of tumors per tumor-bearing animal with diethylnitrosamine.

In a recent Chemical Industry Institute of Toxicology (CIIT) study, rats and mice were exposed to 0, 2.0, 5.6, and 14.3 ppm formaldehyde for 6 hrs/day, 5 days/week, for up to two years. Two hundred and and forty animals were used in each exposure group, out of which 20 animals (at 6 and 12 months) or 40 animals (at 18 months) were selected at random and sacrificed. At about the twelfth month of study, rats exposed to 14.3 ppm formaldehyde started developing nasal cancer (squamous cell carcinoma). By the 18th month of exposure, 37 rats exposed to 14.3 ppm of formaldehyde had developed nasal cancer (Swenberg et al., 1980). Other dose-related changes observed in rats at this time were squamous metaplasia and dysplasia of the nasal mucosa. After 24 months of exposure, the number of rats with squamous cell carcinomas at 14.3 ppm increased to 103 (CIIT, 1982). Additionally, two nasal carcinomas, two undifferentiated carcinomas or sarcomas, one carcinosarcoma and five polypoid adenomas were observed. Of the rats exposed to 5.6 ppm, two had squamous cell carcinomas and six had polypoid adenomas. Eight rats exposed to 2 ppm formaldehyde and one control rat had polypoid adenomas. The adenomas appear to be related to formaldehyde exposure. Two mice exposed to 14.3 ppm formaldehyde also developed squamous cell carcinomas of the nose, but no formaldehyde-related tumors were observed in other exposure groups (CIIT, 1982). No ulceration or nasal tissue inflammation was noted in the study although a second CIIT study did show nasal ulceration for the first 9 days of exposure.

Because mice appear to modify their respiration when exposed to formaldehyde (Barrow, 1980), they may have received only about one half of the exposure that rats received. Thus, the actual exposure of mice at 14.3 ppm may be comparable to that of rats at 5.6 ppm of formaldehyde, indicating that the two species may be developing cancer at a similar rate.

A second 24 month study has recently been completed at New York University in which rats were exposed to 14.6 ppm formaldehyde with and without 10.6 ppm hydrochloric acid. After 18 months, about 10 rats out of 100 in each group exposed to formaldehyde, (with and without hydrochloric acid) developed nasal squamous cell carcinomas, as opposed to none of the animals exposed to hydrochloric acid alone or the control animals (Albert et al., 1982). These results confirm the CIIT finding that formaldehyde causes cancer in animals.

An earlier study conducted at New York University showed 25 of 100 rats developed nasal squamous cell carcinoma when exposed to a mixture of 14.6 ppm formaldehyde and 10.6 ppm hydrochloric acid (Sellakumar et al., 1980). This mixture is thought to contain small amounts of bis (chloromethyl) ether, a known carcinogen that has produced mainly nerve cell tumors (esthesioneuroepitheliomas) of the nose, and squamous cell carcinomas of the lung in rats (Kuschner et al., 1975). Since the concentration of bis(chloromethyl) ether, however, was estimated to be extremely low (less than one part per billion), and since the tumor type and the formaldehyde concentration are similar to those in both of the above studies (CIIT and NYU), it is likely that formaldehyde was the primary carcinogen in this study also.

Epidemiological studies now available (Marsh, 1980; Walrath, 1980; and Wong, 1980) are inadequate to assess the carcinogenic potential of formaldehyde in humans. Wong (1980) and Marsh (1980) studied workers in the formaldehyde industry while Walrath and Fraumeni (1980) examined morticians. In these studies, increases in cancers of the prostate, brain, and Hodgkins disease (Wong, 1980), cancer of the digestive system (Marsh, 1980), cancer of skin, brain, and kidney, and leukemia (Walrath and Fraumeni, 1980) were noted. Only the increase in skin cancer noted by Walrath and Fraumeni was statistically significant. However, these studies did not include sufficient deaths (146 in Wong, 136 in Marsh, and 1106 in Walrath and Fraumeni) for meaningful evaluation. In addition, exposure was not well documented and may not have been of sufficiently long duration.

There are additional reports suggesting increases in the cancers of the larynx (Decoufle, 1979); oral cavity and pharynx (Moss and Lee, 1974); nasal cavity (Bross et al., 1978); and liver and lung (Matanoski, 1980) in occupations where individuals may be significantly exposed to formaldehyde. Exposure to closely related aldehydes, including acetaldehyde, has been associated with upper respiratory tract cancers (squamous cell carcinomas) in exposed workers in an aldehyde factory (Bittersohl, 1974).

Based on the data presented thus far, there is sufficient evidence to conclude, as did the Federal Panel on Formaldehyde (Griesemer et al., 1980), that formaldehyde is a carcinogen in rats and should be presumed to pose a carcinogenic risk to humans. A similar conclusion was reached in October, 1981, by a working group of the International Agency for Research on Cancer (IARC): ..."formaldehyde gas should be considered, for practical purposes, as if it represented a carcinogenic risk to man".

The magnitude of this risk can be estimated by a quantitative carcinogenic risk assessment which depends on assumptions based on current knowledge and theory. It is important to note that although such assumptions are judged to be likely any risk assessment is inherently subject to error, and thus can only convey an idea of the potential magnitude of the risk. An important assumption in any such a risk assessment is that formaldehyde poses a carcinogenic risk to humans. As stated above, although formaldehyde causes nasal cancer in animals, epidemiological data available at present are insufficient to allow any direct conclusions to be made with regard to its carcinogenic effects in humans. Formaldehyde is, however, a direct acting carcinogen whose effects have been observed primarily in exposed tissues with no substantial differences between its metabolism in humans and animals. Additionally, mechanisms of cancer induction are not likely to differ between humans and animals and all human carcinogens (with the exception of arsenic which is thought to be a promoter) are carcinogenic to animals. Based on these findings it is reasonable to assume that formaldehyde can cause cancer in humans.

In order to estimate the risk of cancer associated with low levels of formaldehyde exposure, we chose the multistage model. This choice is based on the widely accepted theory that as a tumor develops, it must progress through a number of stages before reaching a carcinogenic endpoint. The methodology used to estimate this risk has the additional provision that the dose-response curve is linear at low dose, which is predicted if formaldehyde is able to act in addition to other environmental carcinogens or carcinogenic processes in the formation of a tumor. Such interaction is likely since the results of short-term tests, cellular transformation tests, and formaldehyde's ability to react with DNA indicate that formaldehyde (like many other carcinogens) is genotoxic. A particular treatment of the multistage model (a computer program, Global 79, by K. Crump and W. Watson) generates an upper confidence limit (UCL) which incorporates linearity at low dose. We consider estimates based on this UCL, because of the points made above, to be closer to the true risk, in the case of formaldehyde, than that predicted by any other methodology. The Chemical Industry Institute of Toxicology (CIIT) study on formaldehyde exposure of rats is used as the source of the input data. While the dose-response curve for nasal carcinomas from this study is non-linear at high exposure levels, the UCL predicts that within the constraints of the data, linearity can occur below approximately 1 ppm.

The cancer risk is assumed to be proportional to the duration of exposure; it is also assumed that humans and rats are equally sensitive to formaldehyde inhalation. Based on what has been presented thus far, the upper value of lifetime risk from lifetime exposure to a particular formaldehyde level below 1 ppm is estimated to be 0.013 times that level (above 1 ppm, a doubling of the level will more than double the estimated risk). Thus, the upper estimated lifetime risk for lifetime exposure to 1 ppm is 0.013, or about 1 chance in 70 of developing cancer.

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## TABLE II

### Lowest Effective Concentration of Formaldehyde Human and Animal Controlled Studies

| ppm | Length of Exposure | Species | Effect | Reference |
|---|---|---|---|---|
| 0.01 | 5 Minutes | Human | Eye irritation | Schuck et al. 1966 |
| 0.05-0.06 | Minute | Human | Odor threshold | Wahren 1980<br>Melekhina 1964<br>Feldman & Bonashevsyaka 1971 |
| 0.07 | Minutes | Human | Optical chronaxy threshold | Melekhina 1964 |
| 0.08 | 1.5 months | Rabbit | Changes in evoked potential of optic nerve | Bokina et al. 1976 |
| 0.08 | Minutes | Human | Threshold to affect the functional state of cerebral cortex | Melekhina 1964 |
| 0.2 | 1 hour | Human | Eye, nose and throat irritation | Rader 1974 |
| 0.25 | 5 hours | Human | Dryness of nose and throat, decrease in mucous flow rate | Anderson 1979 |
| 0.31 | 1 hour | Guinea pig | Increased airway flow resistance, decreased compliance | Amdur 1959 |
| 0.55 | 10 minutes | rat | Reduction in respiratory rate | kane and Alarie 1977 |
| 0.83 | 3 months | Rat | Histological and histochemical changes in cerebral amygdaloid complex | Bonashevskaya 1973 |
| 0.83 | 1 minute | Human | Altered functional state of cerebral cortex | Feldman and Bonashevskaya 1971 |
| 0.83 | 90 days | Rat | Peribronchial and Perivascular hyperemia, lymphohistiocytic proliferation in lung, focal hyperplasia and RE system activation in cerebral cortex | Feldman and Bonashevskaya 1971 |

TABLE II (continued)

| ppm | Length of Exposure | Species | Effect | Reference |
|---|---|---|---|---|
| 0.83 | 10 minutes | Human | Irritation of upper tract and eyes, accelerated breathing, EEG changes, such as alph rhythm enhancement, changes on automatic nervous system | Sgibnev 1968 |
| 0.83 | 10 months over 2 generations | Rat | Morphological changes in upper respiratory tract, decreased liver weight | Misiakjewicz et al. 1977 |
| 0.83 | Continuous beginning 10-15 days before mating | Rat | Increase in size and number of extramedulary hematopoietic centers, increased epithelial proliferation of common bile duct, increased abnormalities of renal epithelium | Gofmekler et al. 1968 |
| 1.4 | 1 minute | Human | Eye sensitivity to light lowered in unacclimated group | Melekhina 1964 |
| 1.67 | Continuous or intermittent | Guinea pig, rat | Sensitization (inhalation), leucocytosis and change in blood cholinesterase | Ostapovich 1975 |
| 2 | 6 hr/day, 5 day/wk for 18 months | Rat | Epithelial hyperplasia, squamous cell metaplasia of nasal turbinates, rhinitis | Swenberg et al. 1980 |
| 3.8 | 90 days continuous | Rat, dog, rabbit, monkey, guinea pig | Death in 1/15 rats; some inflammation of lungs in all species | Coon et al. 1970 |
| 4.1 | 4 hr/day on days 1-19 of gestation | Rat | Increase in threshold of neuromuscular excitability, peripheral white blood cells, decreased hemoglobin and rectal temperature in pregnant animals | Sheveleva 1971 |

TABLE II (CONTINUED)

| PPM | LENGTH OF EXPOSURE | SPECIES | EFFECT | REFERENCE |
|---|---|---|---|---|
| 4.2 | 1 MINUTE | HUMAN | UNBEARABLE WITHOUT RESPIRATORY PROTECTION | WILEY 1908 |
| 15 | 6 HR/DAY, 5 DAY/WK FOR 24 MONTHS | RAT,<br>MICE | 95 SQUAMOUS CELL CARCINOMAS IN 240 RATS<br>3 SQUAMOUS CELL CARCINOMAS IN 240 RATS | KERNS 1980 |
| 15.5 | 10 HOURS | MOUSE, RABBIT, GUINEA PIG | 5/7 MICE, 3/5 RABBITS, 8/20 GUINEA PIGS DEAD; CLOSED EYES, SLOW DEEP RESPIRATION CONVULSIONS | SALEM AND CULLUMBINE 1960 |
| 41.5 | 1 HR/DAY, 3 DAY/WK FOR 35 WEEKS | MOUSE | UPPER RESPIRATORY TRACT INFLAMMATION, BASAL CELL HYPERPLASIA, EPITHELIAL STRATIFICATION, BRONCHOPNEUMONIA | HORTON ET AL. 1963 |
| 482 | 4 HOURS | RAT | L.C. 50 (APPROXIMATE) | NAGORNYI ET AL. 1979 |

# Carcinogenicity of Formaldehyde

## Final Report

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Report to the American Cancer
Society by the Environmental
Cancer Information Unit
February 25, 1981

ENVIRONMENTAL SCIENCES LABORATORY
MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

## Carcinogenicity of Formaldehyde (Final Report)

The results of a CIIT-sponsored study of the effects on rats and mice of inhalation of HCHO, for periods of up to 24 months were reported in November, 1980. CIIT scientists have published a "Communication" on the results of 18-month exposures of rats to HCHO (henceforth, Swenberg et al., Cancer Research).* However, for information on the 24-month results in rats and mice, we are relying for our review on reports of telephone conversations between Dr. Myra Karstadt of the ECIC staff and Dr. James Swenberg of CIIT, and on the CIIT's "Progress Report on CIIT Formaldehyde Studies," dated December 12, 1980. CIIT expects to publish its final report on the HCHO study within the next few months and it is likely that an article or articles will be submitted for publication in one or more journals.

The CIIT is to be complimented on their policy of speedy dissemination of results from on-going studies of particular interest to the public and the scientific community.

We have also examined for this evaluation the "Report of the Federal Panel on Formaldehyde" (henceforth, Griesemer committee report) published in November 1980. Although that report examined CIIT's data only through 18 months of exposure, the Panel's presentation of results from other experiments and studies has been helpful to us.

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*Swenberg, J.A., et al., Induction of Squamous Cell Carcinomas of the Rat Nasal Cavity by Inhalation Exposure to Formaldehyde Vapor, Cancer Research 40, 3398-3402 (September 1980).

We have attached to this statement copies of all published documents used in our review.

A. Experimental design

Fischer 344 rats and B6C3F1 mice were exposed to HCHO vapor in inhalation chambers for periods of 6 hours per day, 5 days per week for 24 months. The target levels of exposure were 0,2,6 and 15 ppm; measured HCHO concentrations during the first eighteen months of exposure averaged 0, 2.1, 5.6 and 14.1 ppm. 120 animals per sex per species per dose level were used. Interim random sacrifices were carried out at 6, 12 and 18 months. 10 animals of each sex/species/dose level were sacrificed at 6 and 12 months. In the exposed rats, 20 animals of each sex and dose level were sacrificed at 18 months. We do not have precise data on the number of rats sacrificed at 24 months, but we were informed that the number varied with the exposure level.

Survival among the mice was poor due to fighting among the males and urinary tract infections. At 18 months 10 females but no males were sacrificed in the high-dose group because the number of males surviving was very small. Few mice of any dose level were still alive at the end of 24 months. We were not able to obtain precise information on the number of mice sacrificed at each dose level at the end of 24 months of exposure to HCHO.

In case of the group of mice exposed to 15 ppm HCHO, 85 animals were reported to have survived long enough to have had a reasonable

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*A recently-published NIOSH OSHA Current Intelligence Bulletin on formaldehyde exposure is also attached; that document was not used in our review, but it may be of interest.

chance of developing nasal cancers; we are not sure whether this group includes only those animals which survived to 24 months, or whether animals which survived to 18 months or some other time were also included.

## B. Effects of exposure to HCHO-rats

According to published data (Swenberg et al., Cancer Research), in mid-1979, 12 months after exposure to HCHO had begun, three rats exposed to 15 ppm HCHO were found to have squamous cell carcinoma of the nasal cavity. CIIT reported on these cancers in late 1979, noting that historic controls displayed no cancer of this type in approximately 7000 Fischer 344 rats.

By 18 months after the beginning of exposure, 36 rats exposed to 15 ppm HCHO had either died from or, at sacrifice, were found to have, nasal squamous cell carcinomas. At the end of the 24-month exposure period, a total of 95 nasal cavity carcinomas had been found in rats exposed to 15 ppm HCHO.

At 24 months of exposure, 3 squamous cell carcinomas were found in the nasal cavity of rats expored to 6 ppm HCHO. No nasal cancers were found in rats exposed to 2 ppm HCHO or in the control animals.

We understand that pathologic investigation of other organs is not yet completed, but to date no cancers above the spontaneous level have been found in the test or control animals.

C. Effects of exposure to HCHO-mice

At 24 months, 2 mice in the high-level exposure group (15 ppm) were found to have developed squamous cell carcinomas of the nasal cavity. No other mice developed these cancers. Pathologic investigations of other organs in the mice have shown only spontaneous levels of cancer in other organs and tissues.

D. Discussion

There was a good deal of public interest in the CIIT's Fall 1979 report of the 3 nasal cavity cancers and the subsequent report of a total of 36 such cancers in the high-dose rats by 18 months of exposure. In March 1980, in our first report, we reviewed the CIIT data to evaluate their significance for humans.

Last March, we stated that we were unable to draw firm conclusions regarding the significance of the CIIT data. Our uncertainty was attributable, in greatest part, to the occurrence of a viral upper respiratory tract infection (sialodacryoadenitis) in the animal colony at 12 months of exposure. Test and control rats developed symptoms, but mice did not. Because of the viral infection, we could not say with certainty that inhalation of HCHO was solely responsible for the occurrence of carcinomas of the nasal cavity in the 15 ppm rats. We questioned whether the cancers might have resulted from the combined effects of the virus and HCHO.

We have now had the opportunity to examine the available data on the 24-month sacrifices and other deaths. Although possible influence of the viral infection on development of the nasal cancers cannot be completely excluded, given the conditions of the experiment, and given other supporting data, it seems probable that these tumors would have developed in the absence of the viral infection. That is, HCHO exposure and not the viral infection appears to be the crucial factor in development of nasal carcinomas in the CIIT study.

That HCHO, rather than the virus, was crucial in development of the cancers is supported by several findings of the CIIT experiment. Tumors developed only in the HCHO-exposed rats, although both controls and test animals showed signs of infection by the virus. Thus, viral infection alone would not appear to be carcinogenic.

Also, two of the mice exposed to 15 ppm HCHO developed nasal carcinomas by the conclusion of 24 months of exposure. Although data on the mice are only suggestive, because of poor survival of the animals over the 2-year course of the exposures, the mice, which were exposed to the virus but did not develop symptoms of infectious disease, did develop nasal squamous cell carcinomas.

According to published data on the CIIT experiment (Swenberg et al., Cancer Research), three nasal cancers had appeared in the rats by the end of the 12th month of exposure, at about the same time the viral infection occurred in the animal colony. It would be reasonable to assume that these cancers had formed by the time the virus infection occurred. We do not have data on the length of time it takes for nasal carcinomas to develop in the CIIT test system, so we cannot estimate how many other tumors had begun to develop before the infection; such data will, we assume, be obtained in subsequent studies of infection-free animals.

Other factors outside the CIIT studies also support the carcinogenicity of HCHO _per se_. Experiments recently completed at NYU Medical Center involved exposures of Sprague-Dawley rats to a mixture of 14.7 ppm HCHO and 10.6 ppm HCl by inhalation 6 hours/day, 5 days/week, over the lifetime of the animals.* The studies were an outgrowth of earlier research on bis(chloromethyl)ether(BCME). BCME has been shown to be formed by reaction between HCHO and HCl in the air. Although HCHO and HCl could have formed BCME in the NYU studies, the rats developed squamous carcinomas of the nasal cavity rather than the nasal esthesioneuroepitheliomas previously associated with BCME inhalation in Sprague-Dawley rats. Since there were no HCHO controls in these studies, it is not possible to draw any direct conclusions as to carcinogenicity of HCHO alone, but the estimated level of BCME in the inhalation chamber (1 ppb) may have been so low as to render HCHO the major etiologic agent in development of nasal cancers. However, dose-dependent variation in tumor type and the possible significance of BCME exposure cannot be excluded when considering these studies. We look forward to publication of these data. Also, we understand NYU scientists are now conducting studies of rats exposed to HCHO alone.

Formaldehyde is mutagenic in several _in vitro_ assays in species ranging from _Salmonella_ to _Drosophila_. These assays have been used to estimate possible carcinogenicity of chemical substances. Of course, mutagenicity data are only suggestive of possible carcinogenicity, and relationships drawn between results of the in vitro tests and carcinogenicity assume interactions between the substance being tested and DNA or other information macromolecules in the cell. We do not know the mechanism of HCHO carcinogenesis at a molecular level, so we can only see the mutagen test results as interesting and suggestive.

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*In the Griesemer committee report, the exposures were reported on this schedule "for life" (p. 30). In the NIOSH-OSHA Current Intelligence Bulletin, the exposures were reported as "for a total of 544 days" "over a period of 814 days." (p. 5).

Finally, humans as well as rodents develop viral infections of the upper respiratory tract. Although the virus, were it acting as a co-carcinogen or in some other way sensitizing the nasal epithelium to potentiate the effects of HCHO, might render the CIIT assay more sensitive in a quantitative sense, the conditions might not be unlike those found in humans who have both upper respiratory tract viral infections, a not uncommon occurrence, and exposure to HCHO at home or at work. Of course, differences in the human and rodent nose and respiratory systems might make such comparisons inappropriate, but, with data on inhalation of HCHO in rodents and humans somewhat speculative at this time, all possible considerations should be taken into account.

Thus, the virus is, it would appear, at most a co-carcinogen, and we suspect, based on the results of the CIIT studies and other data, that the virus infection did not play a significant role in development of the nasal carcinomas. However, the issue of the virus' activity must remain open until experimental data are obtained which definitely resolve the question.

Based on the 24-month results of the CIIT study, it is clear that HCHO is a carcinogen in rats at levels to which humans are exposed in some work and home environments, and the data in mice, despite uncertainties, indicate that this carcinogenic potential is not confined to one species. Further, the data are very clear-cut and more so than in many other experiments in that the margin between doses at which cancer was found in animals and human exposure is very narrow.

We are very impressed with and concerned about the high incidence of nasal cancer found in the high-dose rats. If rats sacrificed at 6 months (20 total) are excluded from the denominator, then 95/220 animals developed these cancers, an incidence of 43%.

HCHO levels in residences insulated with urea-formaldehyde foam and about which complaints have been filed with government agencies were reported to have ranged from 0.01 to 31.7 ppm. We have attached to this statement some data on levels of HCHO found in several work environments; in several of these workplaces, HCHO levels exceeded 1 ppm, and some were above 5 ppm. Other data on workplace levels of HCHO can be found in the NIOSH Current Intelligence Bulletin, as well as the documents to which we refer in the table "HCHO Levels Measured in Several Environments."

The Griesemer committee reports (p. 46) on several published epidemiologic studies of worker groups, in which there would appear to be some possible connection between HCHO exposures and increased incidence of cancer, including respiratory tract cancer. The worker groups studied included shoemakers, pathologists and textile workers. However, any conclusions drawn from these studies would be, at most, suggestive as regards HCHO carcinogenicity in humans, since these worker groups had exposures to several chemicals other than HCHO and environmental measurements were not available. Several studies are now being conducted of workers with primary exposures to HCHO; results from these studies are not yet available.

## E. Conclusions and recommendations

HCHO is a carcinogen in rats and, data suggest, in mice, at exposure levels comparable to those found in some home and work environments. These findings indicate that effective controls should be initiated to reduce or eliminate human exposures to HCHO. In recommending controls, we emphasize that cancer occurred in animals at levels not unlike those which can be found in some human exposures.

We urge that research be undertaken to elucidate the carcinogenic risk of HCHO exposures in human populations and to elucidate the mechanism or mechanisms by which HCHO causes cancer in rats and mice. We also look forward to reports from CIIT on pathologic examination of other organs, particularly the organs and passageways of the respiratory system, to obtain a better basis for determining whether HCHO is a carcinogen for other tissues.

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We wish to thank the members of the Advisory Committee for their invaluable assistance in the preparation of this report.

## HCHO LEVELS MEASURED IN SEVERAL ENVIRONMENTS

| Environment | ppm HCHO | source |
|---|---|---|
| homes insulated with urea-formaldehyde foam; complaints filed with government agencies | 0.01-31.7 | C |
| embalming rooms | avg. 0.25-1.39 | G,N |
| | range 0.09-5.26 | |
| dress shops | 0.13-0.45 | N |
| clothing store(workroom) | 0.9 -3.3 | N |
| "perma-press"clothing factory | 0.9-2.7 | N |
| nylon fabric coated with urea-HCHO resin(workroom) | 1.0-11 | N |
| paper-conditioning facility(paper treated with urea-HCHO or melamine-HCHO resin) | 0.9-1.6 | N |
| wood-processing plants(USSR) | 2.1-8.9 | N |
| | max. 31.2 | |
| textile plants | 0.1-1.4 | G |
| calf skin tannery-finishing department | 1 -8.6 | G |
| laminating plants which used phenol-resorcinol glues which released HCHO upon curing | one plant-<br>0.04-4.2 | N |
| | other plant-<br>4.2-10.9 | |

C=Consumer Product Safety Commission, Status of Work on Formaldehyde Toxicity and Urea-Formaldehyde Foam Insulation, from Peter W. Preuss, Ph.D., to the Commission, November 2, 1979.

G=Report of the Federal Panel on Formaldehyde, November 1980(transmitted November 21, 1980, by Richard A. Griesemer, Ph.D., Chairman, Formaldehyde Panel, to Susan B. King, Chairman, Consumer Product Safety Commission)

N=Criteria for a recommended standard....Occupational Exposure to Formaldehyde, U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, December 1976.

IARC October, 1981
Meeting

No. 18

3rd draft
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## 4. Summary of Data Reported and Evaluation

### 4.1 Experimental data

Formaldehyde was tested for carcinogenicity by inhalation exposure in two strains of rats and one strain of mice. A significant incidence of squamous-cell carcinomas of the nasal cavity was induced in both strains of rats but not mice. Another study in mice and one in hamsters by inhalation exposure, one in rats by subcutaneous administration and one in rabbits by exposure in oral tanks were considered inadequate for evaluation. Formaldehyde can cause acute degeneration, necrosis, inflammation and increased cell replication in the nasal mucosa of rats and mice following inhalation exposure.

DNA damage has been observed in bacteria, yeast and mammalian cells exposed to formaldehyde. The chemical is mutagenic to bacteria, yeasts and the fruit fly, but not to the silkworm or to mammalian cells in culture. Chromosomal aberrations were seen in formaldehyde-treated mammalian cells, plants and the spermatocytes of grasshoppers and fruit flies. In one study, it induced morphological transformation in mouse 10T½ cells when treatment was followed by exposure to 12-*O*-tetradecanoylphorbol 13-acetate.

One positive and one negative study on formaldehyde-induced dominant lethal mutations in mice have been reported.

Data were insufficient to evaluate adequately the teratogenicity/embryotoxicit of this compound.

### 4.2 Human data

Formaldehyde has been produced commercially since the early 1900s. Its widespread use in a variety of applications (world demand in 1978 is estimated to have been 8862 million kg) is known to result in appreciable exposure of workers and of sections of the general population. Notable recent observations are that formaldehyde is present in the indoor air of buildings and mobile homes containing particleboard made with formaldehyde-based adhesives and in houses insulated with urea-formaldehyde foams.

Three mortality studies of workers manufacturing formaldehyde and other chemicals or using formaldehyde have given inconclusive results. A study of embalmers who used embalming fluid containing formaldehyde showed a proportionate excess of deaths from skin cancer, which increased both with duration of employment in embalming and intensity of exposure (as judged by whether a man was involved only in embalming or also directed funerals). Men involved only in embalming also had increased proportional mortality from cancers of the brain and kidney. ~~There were corresponding deficits at other sites~~. A second study showed a significant excess of deaths from prostatic cancer in the period after 20 years from first employment in a factory. A third study showed a proportionate excess of deaths from digestive-tract cancer in two subgroups of men, but not overall. The total number of deaths or person-years observed after a suitable latent period in all three studies was small and would be insufficient to show an increased risk of an uncommon cancer, ~~in particular of the rare nasal cancer~~.

### 4.3 Evaluation

There is *sufficient evidence* that formaldehyde gas is carcinogenic to rats.

The epidemiological studies provide inadequate evidence to assess the carcinogenicity of formaldehyde to man.

In the absence of adequate epidemiological data, formaldehyde gas should be considered, for practical purposes, as if it represented a carcinogenic risk to man.

DRAFT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
~~DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE~~
PUBLIC HEALTH SERVICE
NATIONAL TOXICOLOGY PROGRAM
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November 21, 1980

Honorable Susan B. King
Chairman, U. S. Consumer
Product Safety Commission
Suite 812
1111 Eighteenth Street, N.W.
Washington, D.C. 20207

Dear Chairman King:

On behalf of the Formaldehyde Panel, I am pleased to submit the Panel's report on the chronic health effects of formaldehyde. May I draw to your attention the Panel's conclusions that formaldehyde poses a cancer risk to humans.

Since the completion of the report, the Panel has been informed that formaldehyde causes cancer in another species, the mouse, and at a lower dose in rats than previously reported. This latest information adds additional weight to the conclusions of the Panel.

Sincerely,

Richard A. Griesemer

Richard A. Griesemer
Chairman, Formaldehyde Panel

cc:
Dr. David P Rall, Director, NTP

Environ[illegible]
Vol. [illegible]

# Report of the Federal Panel on Formaldehyde*

The Federal Panel on Formaldehyde concluded that definitive experiments exist which demonstrate the mutagenicity and carcinogenicity of formaldehyde under laboratory conditions. Formaldehyde induces both gene mutations and chromosomal aberrations in a variety of test systems. Inhalation of formaldehyde causes cancer of the nose in rats. The concentrations of formaldehyde in inhaled air that caused nasal cancer in Fisher 344 rats are within the same order of magnitude as those to which humans may be exposed. The data presently available do not permit a direct assessment of the carcinogenicity of formaldehyde to man. Epidemiologic studies on exposed human populations are in progress and may further clarify the situation. Other experimental and human studies on toxic effects such as teratogenicity and reproductive disorders are as yet inadequate for a health risk assessment.

The CIIT 24 month study on animal carcinogenicity has not yet been completely evaluated. Additional data are expected on the effects of prolonged exposure to lower doses of formaldehyde and on the possible carcinogenicity of formaldehyde in the mouse. The panel recommends that, for a comprehensive health risk assessment, further experiments be conducted on the effects of other modes of exposure (ingestion and skin penetration), the effects in humans, and on the pharmacokinetics of formaldehyde in man and animals and the possible role for formaldehyde in reproductive and chronic respiratory disorders.

It is the conclusion of the panel that formaldehyde should be presumed to pose a carcinogenic risk to humans.

## Introduction

The first evidence that formaldehyde might represent a carcinogenic risk for man was obtained in October 1979 from an ongoing animal experiment conducted by Battelle Columbus Laboratories for the Chemical Industry Institute of Toxicology (CIIT) (*1*). The preliminary results were reviewed by Federal Government scientists, who concurred with the CIIT conclusions. As the experiment progressed and more data became available, the need for a full review of the potential health risks to humans from chronic exposure to formaldehyde became evident.

To accomplish this review, a panel of scientists from within the Federal Government was formed in April, 1980, under the auspices of the National Toxicology Program and coordinated by the Consumer Product Safety Commission. The panel members reviewed and evaluated the available published and unpublished information on the adverse health effects from repeated exposure to formaldehyde. Acute toxic effects and hypersensitivity were not considered, since they had recently been assessed by the Committee on Toxicology of the National Academy of Sciences (*2*).

Nearly seven billion pounds of formaldehyde are produced each year in the United States (*3*), most in the manufacture of urea-, phenol-, acetal-, and melamine-formaldehyde resins. The remainder is used to make other industrial chemicals, agriculture products, leather products, to preserve cosmetics, and to prepare vaccines, drugs, fumigants, and disinfectants. The formaldehyde-based resins are used as adhesives in the manufacture of particle board, veneers, and plywood, and in the production of insulating materials, plastics, protective coatings, textiles, paper, and rubber products.

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Under certain conditions, formaldehyde may be released from some of these products, creating the potential for human exposure to the chemical. Its presence in building materials, such as insulation, particle board, and plywood, as well as in other products, has resulted in complaints to the federal regulatory agencies. For example, the Consumer Product Safety Commission (CPSC) has received a number of complaints from consumers concerning adverse health effects associated with the release of formaldehyde gas from urea-formaldehyde foam insulation (*4*). Consumers have also expressed concern that the high concentrations of formaldehyde within their mobile homes may be unhealthy (*5*). Complaints such as these arise because formaldehyde causes irritation of the eyes, nose, throat, and skin, persistent cough, shortness of breath, nausea, headaches, and dizziness. Similar symptoms have been reported by workers who were exposed to formaldehyde resins that are used in the wood, textile, rubber and leather industries.

In October 1979, federal regulatory and research agencies became greatly concerned about the exposure of humans to formaldehyde when representatives of the Formaldehyde Institute reported preliminary findings from a carcinogenicity study showing that rats exposed to 15 ppm of formaldehyde developed squamous cell carcinoma of the nose (*1*). This concern was reinforced in January, 1980, when representatives of the Interagency Regulatory Liaison Group (IRLG) reviewed the carcinogenicity data in detail (*6*). As a result, CPSC, in cooperation with the IRLG agencies, convened a panel of scientists from eight federal agencies under the auspices of the National Toxicology Program to review health data related to formaldehyde. As part of this review, the panel members were asked to consider the following questions (*7*):

- Is there evidence indicating that formaldehyde may be tumorigenic/carcinogenic at doses other than 15 ppm in the CIIT study?
- Are there confounding factors in the CIIT study such as the irritating properties of formaldehyde, viral infection, special susceptibility of the rat to irritants, or protocol defects? If so, what are the relative merits of these factors?
- What conclusions can be drawn from the tumorigenic/carcinogenic results in the CIIT study?
- What is the applicability of the conclusions drawn in the CIIT study to the human situation?
- What is the relation of animal data from other irritant carcinogens to the human situation?
- How do other formaldehyde studies in animals and epidemiological studies affect conclusions about the human carcinogenicity of formaldehyde?
- Do short-term mutagenicity data support findings of carcinogenicity?
- What conclusions can be reached concerning the potential human carcinogenicity of formaldehyde?
- Are there additional data needed?
- Are these findings relevant to exposure from other routes?
- Is there evidence that formaldehyde is teratogenic or causes reproductive effects?

To address these questions the panel evaluated the published literature and available data from ongoing studies. This report is the result of the panel's review.

## Chemistry and Metabolism

### Chemistry

Formaldehyde, a one-carbon compound with the formula HCHO, has a molecular weight of 30.3 and a boiling point of 19°C. In the gaseous state formaldehyde is a highly reactive chemical with a characteristic pungent odor. It is readily soluble in nonpolar solvents such as chloroform, ether, or toluene but undergoes solvation in polar solvents such as water or methanol. Synthesis of formaldehyde is accomplished typically by the oxidation of methanol in the presence of a copper or silver catalyst.

The common commercial form of formaldehyde (formalin) contains 37–50% formaldehyde in water by weight and is stabilized against polymerization by the addition of 1–15% methanol. Formaldehyde is also commercially available as a solid linear polymer containing 91–95% formaldehyde and 5–9% water (paraformaldehyde or polyoxymethylene) or as a cyclic polymer (trioxane or trioxymethylene). Trioxane, unlike polyoxymethylene, does not readily undergo depolymerization under most conditions.

Formaldehyde undergoes the following chemical reactions in biological systems (*8*):

Hydration in the presence of water:

$$HCHO + H_2O \rightarrow CH_2(OH)_2 \qquad (1)$$

Reaction with the active hydrogen of ammonia, amines, or amides:

$$RNH_2 + HCHO \rightarrow RNHCH_2OH \qquad (2a)$$

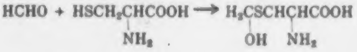
$$RNHCH_2OH + RNH_2 \rightarrow RNHCH_2NHR + H_2O \qquad (2b)$$

$$RCONH_2 + HCHO \rightarrow RCONHCH_2OH \qquad (3a)$$

$$RCONHCH_2OH + RCONH_2 \rightarrow RCONHCH_2NHOCR + H_2O \qquad (3b)$$

These reactions are of particular concern because of the ubiquity of nitrogen compounds (DNA, RNA, proteins, amino acids, etc.) in all biological systems. The reaction with purines and other amines produces an intermediate methylol product which is labile. The reaction product with a second amine moiety is stable.

Reaction with other compounds having active hydrogens such as thiols, nitroalkanes, hydrogen cyanide, and phenol:



$$HCHO + HSCH_2\underset{NH_2}{\underset{|}{C}}HCOOH \rightarrow H_2\underset{OH}{\underset{|}{C}}SCH\underset{NH_2}{\underset{|}{C}}HCOOH \qquad (4)$$

Condensation with HCl (and possibly other inorganic chlorides) in the presence of water to form bis(chloromethyl) ether:

$$2HCHO + 2HCl \rightarrow ClCH_2OCH_2Cl + H_2O \qquad (5)$$

## Metabolism

Formaldehyde can enter the body through inhalation, ingestion or dermal absorption. Absorption of formaldehyde through the upper respiratory tract in dogs has been estimated to exceed 95% of the inhaled dose (*9*). Following oral exposure of dogs to formaldehyde, formate levels in blood increased rapidly indicating rapid uptake and metabolism (*10*). Dermal absorption has also been demonstrated (*11*) but does not appear to be significant in comparison to inhalation or ingestion.

Formaldehyde that enters the body appears to be converted rapidly to formate (*10, 12*) or to combine with tissue constituents by the reactions described above. The conversion of formaldehyde to formate occurs following intravenous (IV) infusion, subcutaneous injection, gastric intubation, or inhalation. Studies using IV infusion of 0.2*M* formaldehyde into dogs have shown that only a small amount of formaldehyde appears in the plasma during exposure (*10*). This becomes undetectable within 1 hr after cessation of infusion. The peak formate concentration following formaldehyde infusion was the same as when formate (0.2*M*) itself was infused. The plasma halflife for formate (between 80 and 90 min) was also similar. Formaldehyde could not be detected after oral administration of 0.2*M* formaldehyde in the same study while formate increased rapidly in the plasma with a halflife of 81.5 min.

Similar experiments on cynomolgus monkeys, in which 0.2*M* formaldehyde was infused IV, likewise showed no accumulation of formaldehyde in blood (*12*). The blood halflife was estimated to be 1.5 min. Similar halflives for blood formaldehyde have been observed in rats, guinea pigs, rabbits and cats (*13*). In a somewhat different experiment, McMartin et al. (*14*) administered $^{14}$C-methanol by gastric intubation. Again, formaldehyde could not be detected although formate levels increased rapidly. A study in which humans were exposed to formaldehyde gas (0.78 mg/m$^3$) for 3 hr also demonstrated a rapid rise in blood and urine formate levels (*15*).

The rapid conversion of formaldehyde to formate occurred in many tissues in the various species examined, including human erythrocytes (*10*), liver and brain; sheep liver; rat brain, kidney and muscle; rabbit brain; and bovine brain and adrenals (*16*). The enzymes involved have been studied by Strittmatter and Ball (*17*) as well as by Uotila and Koivusalo (*16*). The oxidation is initiated by formation of *S*-formyl glutathione which is then oxidized by NAD and finally cleaved by a thiol esterase, releasing formic acid and glutathione. Formaldehyde has also been reported to be oxidized to formic acid by a nonspecific aldehyde dehydrogenase and by the tetrahydrofolic acid pathway (*18*).

Additional studies (*19*) have shown that following subcutaneous administration of $^{14}$C-formaldehyde to rats, approximately 81% of the radioactivity appeared as $CO_2$. A small amount of the radioactivity was found in choline. Almost 60% of a subcutaneous dose of $^{14}$C-formate similarly appeared as $^{14}C$-$CO_2$, with small amounts of radioactivity in choline. Neely (*20*) administered formaldehyde intraperitoneally (IP) to rats and found that 82% of radiolabel was recovered as $CO_2$ and 13-14% as urinary methionine, serine and a cysteine adduct. At lower doses, only methionine was labeled. The author postulated that $CO_2$ was derived from serine (formed from glycine and $N^5$, $N^{10}$-methylene tetrahydrofolate) by deamination to pyruvate and oxidation in the Krebs cycle. The formation of methionine from $^{14}$C-formaldehyde and homocysteine had previously been demonstrated by Berg (*21*). Formation of methionine would also account for the labeled choline observed by DuVigneaud et al. (*19*)

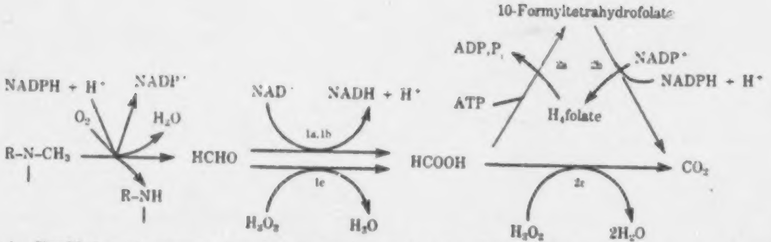

10-Formyltetrahydrofolate
ADP,P$_i$
ATP
2a
2b
NADP$^+$
NADPH + H$^+$
H$_4$folate
NADPH + H$^+$
NADP$^+$
O$_2$
H$_2$O
R–N–CH$_3$
R–NH
HCHO
NAD$^+$
NADH + H$^+$
1a,1b
1c
H$_2$O$_2$
H$_2$O
HCOOH
CO$_2$
2c
H$_2$O$_2$
2H$_2$O

FIGURE 1. Simplified reaction sequence from drug N-demethylation (cytochrome-P-450-dependent monooxygenase) to formaldehyde, formate, and $CO_2$ production. Reactions are: 1a, formaldehyde dehydrogenase (GSH); 1b, aldehyde dehydrogenase; 1c, catalase (peroxidatic mode), 2a, 10-formyltetrahydrofolate synthetase; 2b, 10-formyltetrahydrofolate dehydrogenase; 2c, catalase (peroxidatic mode).

via methylation of phosphatidyl ethanolamine. More recent work by Pruett et al. (*22*) has demonstrated the incorporation of $^{14}$C-formaldehyde into the nucleic acid and protein fractions of WI 38 human diploid fibroblasts. Most of the radiolabel was found in RNA with lesser amounts in DNA and protein. The purine bases of both DNA and RNA were most heavily labeled.

In addition to the serine pathway to $CO_2$ postulated above (*20*), two other pathways have been identified. These are shown in Figure 1 from Waydhas et al. (*23*).

Waydhas et al. (*23*), McMartin et al. (*14*) and Palese and Tephly (*24*) have demonstrated that the catalase reaction (Fig. 1) is not of major importance and that the primary pathway to $CO_2$ from formate occurs via the tetrahydrofolic acid pathway. This has been demonstrated in rat liver perfusates (*23*), monkeys (*14*) and rats (*24*). Since the tetrahydrofolic acid pathway (Fig. 2), from Kitchens et al. (*2*), can

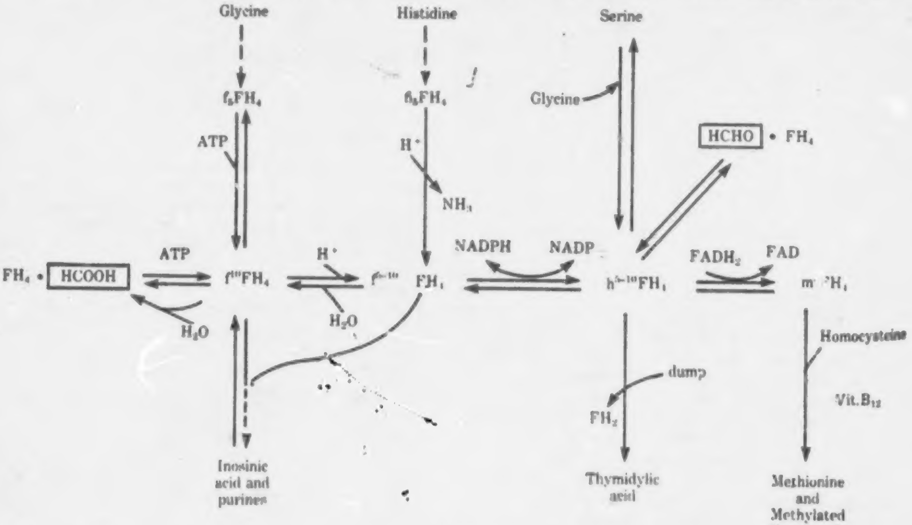

Glycine
Histidine
Serine
f$_5$FH$_4$
fi$_5$FH$_4$
Glycine
ATP
H$^+$
NH$_3$
HCHO • FH$_4$
FH$_4$ • HCOOH
ATP
f$^{10}$FH$_4$
H$^+$
f$^{5-10}$FH$_4$
NADPH
NADP
h$^{5-10}$FH$_4$
FADH$_2$
FAD
m$^5$FH$_4$
H$_2$O
H$_2$O
Homocysteine
Vit.B$_{12}$
dump
FH$_2$
Inosinic acid and purines
Thymidylic acid
Methionine and Methylated Compounds

FIGURE 2. Sources of formate. $FH_4$ = tetrahydrofolic acid; $f^{10}FH_4$ = $N^{10}$ formyltetrahydrofolic acid; $f^5FH_4$ = $N^5$ formyltetrahydrofolic acid: $f^{5-10}FH_4$ = $N^5 - N^{10}$ methylnyltetrahydrofolic acid; $fi^5FH_4$ = $N^5$ formininotetrahydrofolic acid; $h^{5-10}FH_4$ = $N^{10}$ methylenetetrahydrofolic acid.

lead to the transfer of the carbon from formate to a number of other compounds (including serine), it is not clear that the 10-formyltetrahydrofolate dehydrogenase reaction (Fig. 1) is the only reaction of importance for $CO_2$ production in this pathway.

The sources of formate in Figure 2 include the degradation of amino acids such as histidine and tryptophan, and possibly serine and glycine as well. Formaldehyde or formate can also result from *N*-demethylation of drugs such as aminopyrine or ethylmorphine (*23*, *25*) or the metabolism of dihalomethanes (*26*).

Formaldehyde can be formed in mammalian tissues (pig brain and rat kidney) by enzymatic hydrolysis of 5-methyl tetrahydrofolate, in a reaction that appears to require the presence of biogenic amines. The reaction between the amine and formaldehyde is nonenzymatic and leads to the formation of various alkaloids (*27*). A similar reaction involving $N^5$, $N^{10}$-methylene tetrahydrofolate is found in human lymphocytes, brain, kidney, and platelets (*28*); it also apparently requires an amine acceptor. Formaldehyde can additionally result from the action of mixed function oxidases on the *N*-methyl groups of various xenobiotics (*29*). The authors report, however, that the rate of oxidation of formaldehyde to formate is higher than the rate of formation of formaldehyde in the above reaction.

Finally, whereas the conversion of formaldehyde to $CO_2$ occurs in a similar manner in the different species studied, the relative importance of each reaction differs among species and tissues. Thus, the rat is able to convert formate to $CO_2$ at more than twice the rate of monkeys (or man) and, as a result, has lower blood formate levels (*14*) and does not excrete formate in the urine (*20*). Man additionally possesses 50% more hepatic dehydrogenase than do rats (*30*). With regard to tissue differences, Den Engelse et al. (*31*) have shown that mouse (C3Hf/A) and hamster (Syrian Golden) lungs do not convert formate to $CO_2$ as efficiently as liver tissue does.

In summary, free formaldehyde is not usually found in plasma or other body tissues in measurable quantities, such endogenous formaldehyde as is produced may be reasonably presumed to be metabolized rapidly to formate or to enter the one carbon pool. When exogenous exposure does occur, formaldehyde is likewise rapidly metabolized to formate and excreted, converted to $CO_2$ and/or incorporated into other molecules. The same paths seem to occur in all mammalian species examined to date, but reaction rates differ among various species and tissues. Neither the ratio of metabolic deactivation, to tissue or small molecule binding, nor the effect of route of exposure on this ratio is known at this time. Thus, although Egle's work (*9*) suggests that the respiratory tract is the primary area at risk for tumor development, other body sites cannot be ruled out.

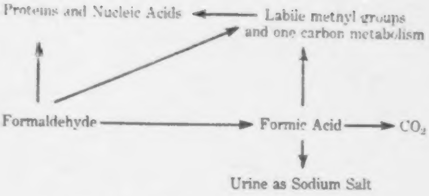

Proteins and Nucleic Acids
Labile methyl groups and one carbon metabolism
Formaldehyde
Formic Acid
$CO_2$
Urine as Sodium Salt

FIGURE 3. Overall metabolism of formaldehyde.

The overall metabolism of formaldehyde is summarized in Figure 3 (adapted from Kitchens et al.) (*8*).

As can be seen from Figure 3, formaldehyde is more chemically active than any of its direct metabolites and would therefore appear to be the chemical substance of most concern for carcinogenicity. The possibility exists, however, as proposed by Poverenny et al. (*32*), that the actual carcinogenic agent may be an amino acid (or other) adduct.

## Teratology and Reproduction

### Reproduction and Teratology Studies in Animals

The effects of formaldehyde or hexamethylenetetramine (HMT) on teratology and reproduction in laboratory animals have been studied using four methods of administration: inhalation, oral gavage, dietary, or in drinking water. Because the method of administration might have affected the results, the studies are presented chronologically for each method. Hexamethylenetetramine (HMT), an antimicrobial food additive, degrades to formaldehyde and ammonia in an acid medium or in the presence of protein, as in the digestive tract (*33*).

***Inhalation Studies.*** Gofmekler and his colleagues studied the teratogenic and toxic effects of formaldehyde in 36 female rats (12 per group) exposed to 0, 0.012 or 1.0 mg/m$^3$ from 10 to 14 days before impregnation through gestation. Three male rats per dose level were also exposed for 6-10 days before they were mated.

Gofmekler (*34*) reported the effect of formaldehyde on fertility, fetal weights and organ weights. In both treated groups, formaldehyde caused a 14-15% increase in the length of gestation; it also increased the average body weight of the offspring and their heart, adrenal, and kidney weights. These changes might have resulted from the extended gestation time. In contrast, the liver and lungs from pups in the treated groups weighed less than those of the control pups. Although Gofmekler stated that there was a decrease in the litter size, his data suggest that this may not be accurate. Our calculations, based on data in Gofmekler's article, show that groups exposed to 0.012 and 1.0 mg/m$^3$ of formaldehyde had average litter sizes of 19.6 and 17.3 pups, respectively, as compared to the control value of 11.2. These calculations assume that all females in each group became pregnant. Gofmekler stated that some females in each group did not become pregnant, but did not report the details. This implies that several dams produced over 20 pups each.

Gofmekler, Pushkina and Klevtsova (*35*) reported data related to changes in the developing embryo. Identical data were reported by Pushkina, Gofmekler, and Klevtsova (*36*). They measured ascorbic acid in whole embryo, placenta, maternal liver and fetal liver; "nucleic acids" (apparently RNA) in maternal liver, fetal brain and fetal liver; and DNA in maternal and fetal liver. Significant decreases in ascorbic acid concentrations occurred in the whole embryo and in the maternal liver at both dose levels. A significant increase in ascorbic acid concentration in liver occurred in offspring from dams exposed to 0.012 mg/m$^3$. RNA concentrations in maternal livers were greater at both dose levels than they were in controls. RNA concentrations of fetal brain were similar in control and treated groups. DNA content was significantly lower in maternal and fetal liver in both treated groups than in control animals. The authors concluded that formaldehyde "significantly inhibited the synthesis of nucleic acids." This conclusion is not, however, supported by the data in the article.

Gofmekler and Bonashevskaya (*37*) reported the data related to histopathological changes in the liver and kidneys of fetuses from dams exposed to formaldehyde. The hepatic changes included an increased proliferation of epithelial cells in the bile duct and segmented forms in the hepatic sinusoids. The kidney changes included renal epithelial cells with polymorphic nuclei, casts in the lumina of some tubules, and functional alterations in the renal tubule apparatus. Exposure to 1.0 mg/m$^3$ of formaldehyde also caused a decrease in myocardial glycogen, an involution of the thymic lymphoid tissue and disintegration of lymphocytes. Histologically, the testes of adult males exposed to formaldehyde were similar to those of the controls.

From macroscopic evaluation it was reported that formaldehyde inhalation by pregnant dams did not affect embryonic or fetal development.

Sheveleva (*38*) studied the teratogenic potential of formaldehyde in pregnant albino rats. The rats were exposed to 0.005, 0.0005 or 0 mg/l of formaldehyde for 4 hr each day on days 1-19 of gestation. Fifteen females per group were killed on day 20, while six were kept to obtain progeny. On day 17 of pregnancy, body weight, spontaneous mobility, rectal temperature and hemoglobin, leukocyte, and erythrocyte concentrations were measured. On day 20, corpora lutea, implantation sites, pre- and post-implantation deaths, and living fetuses were counted. The sizes and weights of living fetuses were determined.

Dams exposed to 0.005 mg/l of formaldehyde exhibited decreased neuromuscular excitability, spontaneous mobility, rectal temperature, and hemoglobin concentration. Exposure to 0.0005 mg/l only caused a slight increase in lymphocytes.

At sacrifice on day 20, the number of preimplantation deaths was higher in both groups exposed to formaldehyde than it was in the controls. Interestingly, the number of live fetuses was approximately the same in all groups. No external malformations were observed in the offspring.

Six dams from each group delivered offspring on day 22; all progeny appeared to be normal at birth. At one month postpartum, the female offspring from control dams were larger than the female offspring from treated dams. For male progeny, the opposite was true. At one month, the spontaneous mobility of progeny from treated dams was less than that of control progeny. By two months, the hemoglobin and leukocyte concentrations were decreased in progeny of dosed dams but not in a dose-related manner.

Guseva (*39*) studied the gonadotropic effects of formaldehyde by measuring testicular nucleic acid content in rats. During a 6 month treatment period, 3 groups of male rats were subjected to a combined action of formaldehyde orally (in drinking water) and by inhalation. Group 1 received formaldehyde at a concentration of 0.1 mg/l in drinking water and by inhalation at a level of 0.5 mg/m$^3$. Group 2 received formaldehyde at a concentration of 0.01 mg/l and by inhalation at a level of 0.25 mg/m$^3$. Group 3 received formaldehyde at a concentration of 0.005 mg/l and by inhalation at a level of 0.12 mg/m$^3$. Group 4 served as untreated controls. Treatment in the drinking water was continuous and simultaneous exposure to formaldehyde by both routes occurred five times per week for 4 hr each time. Reproductive function was evaluated by pairing each treated male with two virgin untreated females. Although the number of males was not specified, the use of six females per group implies the use of three males in each group. On day 20, an unspecified number of pregnant females were killed and their offspring were removed and examined. Guseva failed to mention the results of the examination of the fetuses. The remaining dams were allowed to produce offspring. The number and weight of newborn rats were recorded. Observations of their subsequent development extended over one month. The time of eye opening and other developmental indices were recorded for the offspring of males in groups 1 and 3 only.

The capacity of the treated males to produce offspring was not diminished. There was no effect on the weight of the fetuses or the size of the litters. The offspring were morphologically normal at birth and developed normally thereafter. Gonadotrophin levels were not significantly different between males in the control group and those in the treatment groups. However, the amount of nucleic acid in the testes of males of groups 1 and 2 was significantly less than the amount in the testes of the controls.

Sanotskii et al. (*40*) studied the effects of formaldehyde on reproduction in an unspecified strain and number of albino rats. They exposed groups of pregnant and nonpregnant rats to 0, 0.4 or 6.0 $mg/m^3$ of formaldehyde for 4 hr/day for 20 days. Evaluations were made of body weight, nervous system function, renal function, hepatic function, and biliary levels of cholic acid. Blood parameters, oxygen uptake, and rate of respiration were measured.

Nonpregnant animals were more susceptible to the effects of formaldehyde than were pregnant animals. Formaldehyde at 6.0 $mg/m^3$ resulted in altered renal function as shown by decreases in daily diuresis and urinary chlorides and an increase in urinary protein concentration. The increase in urinary protein may have reflected decreased urinary output. Altered hepatic function was manifested by a decrease in urinary excretion of hippuric acid. At 6.0 $mg/m^3$, only blood hemoglobin decreased in the pregnant rats. Exposure to 0.4 $mg/m^3$ did not produce toxic changes in either pregnant or nonpregnant rats.

All the studies suffered from an unreported or inadequate number of animals treated per dose level. In the teratology studies, detailed results from skeletal and soft-tissue analyses were missing. None of the studies had a sufficient number of dose levels to fulfill current requirements. Even with these deficiencies, there were indications that formaldehyde might affect reproductive potential by altering testicular nucleic acids and by increasing pre-implantation losses.

***Dietary Studies.*** Hurni and Ohder (*41*) studied the effects of formaldehyde on reproduction in the beagle. Groups of 9-11 pregnant bitches were fed dietary levels of 600 or 1250 ppm HMT, or of 125 or 375 ppm formaldehyde, from 4 days after mating to day 56. Eleven control dogs ate unadulterated chow. The bitches were weighed weekly. The pups were weighed at birth and twice weekly thereafter. They were inspected for visible defects immediately after birth and at 8 weeks postpartum. Stillborn pups and those that died before weaning were autopsied and examined for internal and skeletal anomalies.

Neither formaldehyde nor HMT affected the pregnancy rate. Maternal body weights increased normally during pregnancy in all groups. The duration of gestation was not affected by formaldehyde or HMT. Mean litter sizes were within the normal range for all groups. In the group that received 1250 ppm of HMT, there was a greater percentage of stillborn pups than in any other group; this was mainly due to one litter in which 7 of 9 pups were dead. The stillborn pups were not malformed.

During the first month, the pups from bitches given 1250 ppm HMT grew less than normal. The retarded growth coincided with increased mortality. In the same group, the percentage of pups that survived to weaning was lower than it was in the other groups. All the dogs that were observed for up to 9 months exhibited normal behavior, appearance, mobility, and muscular coordination.

Natvig, Andersen and Rasmussen (*42*) studied the effects of HMT fed to Wistar rats. Two groups of 16 male and 16 female rats each were fed a diet containing 0.0 or 0.16% HMT starting at 2 months of age and continuing for three months, when they were mated with group mates. Their offspring were fed the same diet. The offspring were weighed at 7 and 15 weeks, measured for voluntary muscle activity at 6 weeks, and killed when they were 123 days old. Half of them were autopsied.

There were no detectable differences between the test and control groups. The fertility of the treated animals was similar to that of control animals. The offspring from both groups had similar muscular activity, body weights, general health and organ weights.

For the purpose of clarifying the teratogenic potential of formaldehyde, it is unfortunate that in both of these studies the dams were allowed to deliver naturally. Removing all the pups by cesarean section would have permitted detailed examination for anomalies. By allowing the dams to litter, it was possible that the malformed pups were eaten by the mother before being seen by the investigator. Neither report states if an observer was present at all deliveries. Although teratogenic effects were not noted. HMT appeared to have fetotoxic and postnatal effects in the beagle at 1250 ppm (31 mg/kg). In the rat study, additional dose levels would have been desirable.

***Intubation Studies.*** Marks, Worthy and Staples (*43*) intubated pregnant outbred albino mice on days 6-15 of gestation with 1% aqueous formaldehyde at levels of 0, 74, 148, or 185 mg/kg/day. On day 18, the mice were killed and the offspring examined. All mice were coded in a manner that prevented laboratory personnel from knowing which ones belonged to the control and test groups. Visceral observations were made by the Staples technique and all fetuses were examined for skeletal anomalies.

Formaldehyde was toxic to 22 of 34 pregnant mice at 185 mg/kg. At 74 mg/kg, there was a significant decrease in average weight gain during pregnancy. Formaldehyde treatment, at any dose level, did not result in malformations.

Although formaldehyde caused toxicity in pregnant mice, it was not teratogenic. Because of the methods employed and the number of animals used at each level, this appears to be a valid, reliable, and negative teratogenic study of orally administered formaldehyde.

***Drinking Water Studies.*** Della Porta, Cabral and Parmiani (*44*) conducted several studies on the effects of HMT in rats and published results in a single manuscript.

In the short-term reproduction and toxicity experiment, 12 females and 6 males were given a solution of 1% HMT in the drinking water, beginning at 8 weeks of age. Two weeks later, the animals were mated (2 females: 1 male) and treatment of the females was continued during pregnancy and nursing. Twenty-four males and 24 females were randomly selected from the progeny and treated as above until 20 weeks post partum. Each animal was weighed weekly. At the end of treatment, the animals were sacrificed, their organs were weighed, and histological examinations were conducted. Groups of 12 untreated dams and 48 pups were used as controls.

All treated females and 11 of 12 control females became pregnant and produced 124 and 118 offspring, respectively. The progeny of the treated females were not malformed. The mean body weights of the treated males and females were significantly less than those of controls. These differences lasted up to 9 weeks for males and to 13 weeks for females. After these times, body weights became comparable to the control values. When the offspring were autopsied at 22 weeks, no microscopic or macroscopic lesions were seen. Body weights and organ weights (liver, kidneys, spleen, thymus, pituitary, adrenals and testes) were similar for treated and control groups.

In the second experiment, two females and one male were given a solution of 1% HMT in the drinking water before mating. The treatment of females continued until two litters of 10 rats each had been weaned. Treatment of the $F_1$ progeny continued until they were 40 weeks of age. To produce an $F_2$ generation, seven $F_1$ females were mated with three $F_1$ males at 26 weeks of age. $F_2$ animals were mated at 15 weeks of age to produce an $F_3$ generation. $F_1$ and $F_2$ animals were given HMT until the 40th week postpartum; $F_3$ animals were given HMT to the 20th week. $F_1$, $F_2$ and $F_3$ animals were observed for 130 weeks (2.5 years). All survivors were sacrificed when they reached 3 years of age.

The survival rates of all the generations of offspring were not affected by treatment. Mean body weights, obtained many times during the experiments, showed no significant differences between control and treated groups.

In another study, five adult female rats were bred and treated with 2% HMT in the drinking water until 49 offspring were weaned. The offspring were treated with 2% HMT until they were 50 weeks of age. After treatment, the survivors were observed until 130 weeks of age. Rats (48 males and 48 females) from a previous study served as controls; they were observed until they were 3 years of age. Mean body weights were not significantly different between treated and control animals.

All three studies lacked a sufficient number of animals per dose level and number of dose levels to permit a meaningful evaluation of the potential of HMT to affect reproduction of fetal development. The third study also lacked appropriate concurrent control animals.

## Reproduction and Teratology Studies in Humans

Shumilina (*45*) studied the reproductive potential of women who were exposed to formaldehyde. In the study, the menstrual and reproductive functions of 446 women were evaluated in two experimental groups. The first group of 130 women were fabric trim shop finishers. The second group of 316 women were fabric warehouse inspectors. A third group of 200 industrial goods saleswomen who were not exposed to formaldehyde were used as controls. The trim shop finishers worked in atmospheric concentrations of formaldehyde ranging from 1.5 to 4.5 mg/m$^3$. The warehouse inspectors worked where formaldehyde concentrations varied from 0.3 to 0.7 mg/m$^3$ in one shop and from 0.05 to 0.1 mg/m$^3$ in another shop. All women were given complete medical examinations.

Menstrual disorders were found in 47.5% of the women exposed to formaldehyde as compared to 18.6% of the controls. Dysmenorrhea was found in 24.3% of the finishers as compared to 9.2% of the controls and 20.2% of the inspectors. It occurred more frequently in the 31-40 year-old women (20.7% in the experimental group versus 6.7% in the controls). A cause of the painful menstruation was not found. Hypomenstrual syndrome occurred in 1.2% of the finishers with less than 5 years of potential exposure to formaldehyde, in 47% with 6-10 years of potential exposure, and in 6.8% of cases with more than 10 years of potential exposure. More menstrual disorders were found in workers below 30 years of age (33.4%), but fewer disorders were observed in persons aged 30-40 years (20.8%).

The incidence of inflammatory diseases in the reproductive tract among trim shop finishers was 38.2% and among the warehouse inspectors it was 25.1%. Both of these values were greater than the control value ($p < 0.05$). The percentage of women with exposure to formaldehyde who had primary sterility was 5.2; this value may be compared to 2.5% incidence in the controls. The incidence of secondary sterility was 15.3% in the finishers, as compared to 6.5% in the controls. The high incidence of secondary sterility in exposed women may have been due to previous inflammatory diseases.

The number of term deliveries and artificial abortions did not differ significantly among the groups of workers investigated. Anemia, the most frequent complication of pregnancy, occurred twice as often in women exposed to formaldehyde, as it did in control women. The hazard of intrauterine asphyxiation of the fetus was also encountered twice as often in the exposed women as in the control group. The percentage of children with low birth weights was greater in women exposed to formaldehyde than it was in the control women.

Menstrual disorders were found in women exposed to formaldehyde. Although the number of term births and artificial abortions did not differ among the groups, there were increases in primary and secondary sterility, anemia, and intrauterine asphyxiation of the fetus among women exposed to formaldehyde. Though these data have many limitations, they raise the possibility that formaldehyde may affect human reproductive processes. Additional research is needed to confirm these effects.

## Reproduction-Related Studies

Palkovits and Mitro (*46*) studied formalin-induced stress in neonatal rats. They injected one group of newborn Wistar rats with 0.02 ml of 2% formaldehyde IP once on the day of birth. A second group was injected daily for the first 4 days after birth. Control animals were untreated. At 24 hr after the last injections, all neonates were decapitated. The adrenals and hypothalamus were examined microscopically.

In the neonates injected for 4 days, degenerative cellular atrophy occurred in the ventro-medial arcuate of the hypothalamus. Single injections of formaldehyde did not cause degenerative changes but did cause decreased cellular activity in the medial field of the ventromedial nucleus and the arcuate nucleus and an accumulation of granules in the neuronal cytoplasm. In both groups, formaldehyde injections increased nuclear volume in the adrenals. These changes indicate that the hypothalamus of the neonatal rat is sensitive to corticoid feedback induced by formaldehyde administration.

Cohen (*47*) studied the response to formaldehyde injection in fetal rats by measuring ascorbic acid levels in the adrenals. Pregnant female rats were anesthetized with ether and delivered by cesarean section. The first fetus from each litter served as the control. Approximately 6 µl/g of 2% formaldehyde were then injected SC into one or more litter mates. Fetuses were injected with formaldehyde at 18.5, 19.5, 20.5 or 21.5 days of gestation.

Injections of formaldehyde resulted in decreased ascorbic acid levels in the adrenals at 20.5 days of gestation. Injections on other days of gestation did not cause this response in fetuses.

Conner et al. (*48*) studied the effects of formaldehyde injected into the uterus of pregnant rats. They were interested in its potential as a contragestational agent. On day 3 or day 7 after mating, they injected 0.05 ml of formaldehyde (40, 10, 7, 3.5, 2.0, 0.5, 0.05 or 0.0005%) into one uterine horn and 0.09% saline into the other horn (control) of 3-5 pregnant Sprague-Dawley rats/group. All solutions of formaldehyde also contained 12-15% methanol. On day 15, dams were sacrificed, and the number of corpora lutea, viable fetuses, and resorptions were counted.

Injections of 40 and 10% formaldehyde produced maternal toxicity and death. Injections of 7.0 through 0.5% on day 3 terminated most pregnancies. When these concentrations were injected on day 7, most pregnancies continued. The authors concluded that the contragestational properties of formaldehyde were similar to those of other protein denaturing agents, including ethanol, methanol and silver nitrate. Because methanol solutions alone were not tested, contragestational effects of methanol could not be clearly distinguished from those of formaldehyde.

These physiological and endocrine studies are interesting but their relation to the teratogenic potential of formaldehyde is unclear.

## Dominant Lethal Studies

Epstein et al. (*49*) tested formaldehyde for mutagenicity by the use of the modified dominant lethal test. Male ICR/Ha Swiss mice were given a single dose of 16, 20, 32 or 40 mg/kg of formaldehyde IP. After dosing, each male was placed with three females weekly for 3 weeks. Alternatively, male ICR/Ha Swiss mice were given dose levels of 16 or 20 mg/kg IP and placed with three females weekly for 8 weeks. At the dose levels tested, formaldehyde did not produce an increase in early fetal deaths or pre-implantation losses.

Formaldehyde did not appear to affect spermatogenesis or fertility in mice at the dose levels tested in this study.

## Recommendations

***Teratology.*** The data are inadequate to demonstrate whether or not formaldehyde is teratogenic. The panel's survey revealed only one well-conducted study and that was done by oral administration in mice (*43*). Recommendations are that teratology studies should be performed in rats and rabbits and that these studies should include the administration of formaldehyde by inhalation.

***Animal Reproduction.*** The study of Della Porta et al. of HMT (*44*) lacked the proper number of animals per group needed to evaluate reproductive and teratogenic effects. Multigeneration studies with a larger number of animals should be conducted to test the effects of formaldehyde on reproduction.

Although the physiological and endocrine studies contribute to an understanding of the reproductive effects of formaldehyde, many questions remain unanswered. Mechanisms of biochemical changes and teratology cannot be elucidated until additional biochemical and pharmacological studies are done including placental transfer studies.

***Human Reproduction.*** Shumilina's study (*45*) revealed several possible effects of formaldehyde on human reproduction, but the study lacks sufficient data to answer the questions it raises. Controlled epidemiological studies should be conducted.

# Mutagenicity

In a review of the extensive literature on the genetic toxicology of formaldehyde by Auerbach et al. (*50*), the results of experiments on formaldehyde-treated food in Drosophila are discussed as well as data obtained by exposure of other organisms to vapor or aqueous solutions of formaldehyde and by combination treatments with formaldehyde and other mutagens. Formaldehyde treatment alone gives positive but weak responses in many laboratory organisms; both gene mutations and various types of chromosome aberrations are produced. A brief summary of the genetic effects of formaldehyde has also been published by Cooper (*51*).

## Genetic Effects of Exposure

***Formaldehyde-Treated Food.*** The most extensive data (*50*) have resulted from treatment of Drosophila with formaldehyde-food (FF). In the early experiments of Rapoport (*52*) treatment of young larvae resulted in an increase of sex-linked recessive lethals from a control frequency of 0.2% to about 6%. FF produced all types of gene mutations (both point mutations and deletions) and chromosome rearrangements (small duplications and deficiencies to inversions and translocations). These results were independently confirmed by Kaplan (*53*). Slizynska (*54*) compared the structural changes induced by FF with those produced by x-rays. In contrast to 97% translocations or inversions and fewer than 3% small deficiencies or duplications induced by x-rays, only 30% translocations or inversions and 64% small duplications or deficiencies were found among FF-induced changes.

***Formaldehyde Vapors.*** No mutations were produced by exposing Drosophila adults for up to 1 hr or larvae for up to 2 hr to sublethal concentrations of formaldehyde gas (*55*).

***Formaldehyde Solutions.*** Early experiments in *Escherichia coli* B (*56*) showed that formaldehyde is a very weak agent for the production of point mutations from streptomycin-dependence to independence. Injection of formaldehyde solutions into adult Drosophila provided an effective means for inducing sex-linked recessive lethal mutations, but lower frequencies were found than obtained with FF (*57*, *58*).

More recent studies have shown that the ability of formaldehyde to induce forward mutations at specific loci in the *ad*-3 region of Neurospora (by direct treatment at levels producing 75 - 5% survival) increased from a spontaneous frequency of $0.4 \times 10^{-6}$ to $4 - 6 \times 10^{-6}$ among survivors (*59*). With this assay, gene mutations resulting from both point mutations and multilocus deletions can be detected. Genetic characterization of formaldehyde-induced *ad*-3 mutants is in progress. Formaldehyde was found to induce point mutation by reverse-mutation in both Neurospora (*60*, *61*) and Aspergillus (*62*), but not in Salmonella (*63*, *64*). The National Toxicology Program has reported that, in recent investigations by three independent laboratories using the Ames test, formaldehyde tested positively in one of four bacterial strains (TA 100) that detects base-pair substitution mutations.

A number of genetic effects have been found in mammalian cells in culture. These include: (1) an 8-10 fold increase in forward mutation frequency at the thymidine kinase (TK) locus in mouse lymphoma cells (*65*); (2) a 1.5–3-fold increase in the frequency of sister chromatid exchanges in Chinese hamster ovary cells and in human lymphocytes in culture (*66*); and (3) induction of unscheduled DNA synthesis in HeLa cells over a dose range of $10^{-6} - 10^{-8}$ *M* (*67*).

***Mammalian* in vivo *Studies.*** No data were found in the literature on the induction of genetic damage in mammals either in somatic cells or germ cells. Epstein et al. (*68*) were unable to detect early fetal deaths induced by formaldehyde injection in an assay for dominant lethality in mice.

***Interaction with Other Mutagens.*** In Drosophila, Sobels (*69*) found that either pre- or post-treatments with formaldehyde almost doubled the frequencies of x-ray-induced sex-linked recessive lethals. In Neurospora, early experiments by Dickey et al. (*70*), Kolmark (*71*), and Kolmark and Westergaard (*72*) showed that formaldehyde by itself is only weakly mutagenic, whereas a mixture of formaldehyde and peroxide gave a much higher effect than could be predicted on the basis of a strictly additive effect of the two agents.

***Increased Effects in Repair-Deficient Strains.*** Nishioka (*73*) compared the lethality and mutagenic damage produced by formaldehyde in *E. coli* strains HCR+ and HCR- and found that, in the latter excision-repair deficient strain, much higher levels of effect were produced. Comparisons of the ability of direct treatment with formaldehyde solutions to induce specific locus mutations in the *ad*-3 region of wild-type and excision-repair deficient, two-component heterokaryons of Neurospora have shown up to a 370-fold higher mutation frequency in the excision-repair deficient strain (*59*). The same is true for excision-repair deficient mutants of *Saccharomyces cerevisiae* (*74*). In addition, more pronounced genetic effects of formaldehyde were found with cell lines of *Xeroderma pigmentosum* as compared with normal human fibroblasts in culture (*75*).

## Summary

Formaldehyde produces gene mutations and such chromosome aberrations as deficiencies, duplications, inversions, and translocations; no data are available for the production of aneuploidy. In most experiments, dose-response relationships could only be demonstrated with difficulty or not at all, and all data are consistent with the classification of formaldehyde as a weak mutagen. Formaldehyde has been shown to interact with other mutagens such as x-rays, ultraviolet radiation and hydrogen peroxide, and to at least double the frequencies of mutants expected from treatment with these agents. Formaldehyde effects on both lethality and the induction of mutations in microbes are markedly enhanced in excision-repair deficient strains. No data are available from studies on mammalian systems *in vivo* on genetic effects on germ cells.

## Risk Assessment

Since there are no effects reported on mammalian germ cells the genetic risk of exposure to formaldehyde can only be made by extrapolation from experiments with other laboratory organisms. The only genetic data relevant for risk estimation are those for the induction of gene mutations and chromosome aberrations. There are no data on the induction of aneuploidy by nondisjunction or any other mechanism. In this respect, the most extensive data result from experiments with Drosophila on formaldehyde-treated food. It is not known how representative these data are of genetic effects that would be expected from exposures to vapors or solutions. The Drosophila data show that 64% of the transmitted chromosomal effects studied resulted from small duplications or deficiencies, the remainder were due to large inversions and translocations. No data were found which would be useful in determining whether a comparable spectrum of genetic alterations would be found with lower chronic levels of exposure. In conclusion, although heritable genetic damage has been demonstrated, only small increases would be expected from the levels of formaldehyde which might reach the germ cells. The Drosophila data, for example, indicate that sensitivity is limited to effects on males and is restricted to early spermatocytes; whether similar effects can be expected in whole animal systems is unknown.

## Recommendations for Future Studies

The genetic effects of formaldehyde in man could be more readily predicted if selected experiments were performed on laboratory animals. Such studies could begin with an experiment using the *in vivo* mammalian spot test to determine whether formaldehyde vapors or solutions would cause gene mutations in somatic cells that affect coat color (*76*). This test has the advantage of requiring exposure and analysis of progeny from only 30-50 pregnant females. The test is thus relatively inexpensive and has been used to evaluate the mutagenic activity of a wide range of chemical agents.

In the event of a positive result in the mammalian spot test, two additional assays should be applied in mice: (1) the heritable translocation test (*77*) and (2) the morphological specific locus test (*78*). Considerably more work is involved in these two assays but they are useful to determine, respectively, whether heritable chromosome aberrations and gene mutations have been produced. In the presence of a negative spot test it is unlikely that positive results would be found in the latter two tests which detect genetic effects produced in male germ cells.

## Carcinogenicity

The literature search revealed only a few studies that were designed for the purpose of testing formaldehyde for carcinogenic activity. Because of limitations in experimental design, many of the reported studies are inconclusive. In this section only those studies will be reviewed which were conducted over a sufficient length of time to permit detection of carcinogenic activity activity of the test chemical. The investigations will be discussed in order of their importance as judged by this panel, starting with the inhalation exposure studies.

### Review of Formaldehyde Carcinogenesis Studies

By far the most important carcinogenesis study conducted to date with formaldehyde is the CIIT inhalation study recently reported by Swenberg et al. (*79*). F344 rats and B6C3F$_1$ mice (120 male and 120 female rats or mice per group) were chronically exposed to 2.1, 5.6 and 14.1 ppm of formaldehyde vapors for 6 hr/day, 5 days/week. During the first 18 months of exposure, 2, 2, 8 and 44 rats died in the groups exposed to 0, 2.1, 5.6 and 14.1 ppm of formaldehyde, respectively. Of the 44 rats which died spontaneously in the group exposed to 14.1 ppm, 32 had nasal tumors (28 squamous carcinomas and four squamous papillomas). Many of the rats also showed hyperplastic and metaplastic lesions of the nasal epithelium. Hyperplastic and metaplastic lesions were also detected in rats exposed to 5.6 ppm formaldehyde (14 lesions were found in eight rats), indicating that the nasal epithelium was significantly damaged at this lower level of exposure. At 18 months of exposure, 40 rats were killed in each group. Eight of 40 rats exposed to 14.1 ppm had developed nasal squamous carcinomas. Although no carcinomas of the airways were found in the other groups, one adenomatous polyp was found in one rat of each of the groups exposed to 2.1, 5.6 and 14.1 ppm. In addition, a large number of hyperplastic and metaplastic lesions was detected in the nasal epithelium of these rats, even at formaldehyde concentrations as low as 2.1 ppm. No exposure-related tissue abnormalities were reported at sites other than the nasal cavities and no exposure-related neoplasias were reported in formaldehyde exposed mice, but examination of the animals sacrificed after 24 months of exposure is not complete.*

One complication noticed during the study was a spontaneous outbreak in rats of sialodacryoadenitis. The evidence for this consisted of decreased body weight in all dosed and control rat groups at about the 52nd week of the experiment, followed by prompt recovery of body weight, and histopathological demonstration of typical lesions in lacrimal and salivary glands and in the upper respiratory tissues of dosed and control rats in the 12 month sacrifice groups. Evidence of sialodacryoadenitis was not found in rats sacrificed at 6 or 18 months or in those with unscheduled deaths. Virus isolation, viral antigen demonstration, and serologic tests for antibodies were not attempted in rats or mice.

With regard to formaldehyde in the exposure chamber, a panel of experts reviewed the method of formaldehyde generation and monitoring and "agreed that the Battelle approach to formaldehyde vapor generation was a suitable adaptation of accepted methods and principles and, therefore, was sound and based upon the best available technology. The same type of assessment applied to the chamber air monitoring system, which also combined two well-established procedures" (*81*).

Suggestive evidence for the carcinogenicity of inhaled formaldehyde vapors also comes from a study by Laskin et al. (*82*). One hundred male Sprague-Dawley rats were exposed to a mixture of gaseous formaldehyde (14.7 ppm) and hydrogen chloride (10.6 ppm) for 6 hr/day, 5 days/week for life. Of the exposed rats, 27% developed nasal tumors, of which 25 were squamous carcinomas and

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*The Chemical Industry Institute of Toxicology recently reported results up to and including the 24 months sacrifice, as follows: in rats exposed at 14.1 ppm there were 93 animals with squamous cell carcinomas, four with squamous papillomas, three with adenomatous polyps and two with carcinomas of the respiratory epithelium; at 5.6 ppm there were two squamous cell carcinomas, four adenomatous polyps and one carcinoma of the respiratory epithelium; and at 2.1 ppm, five rats had developed adenomatous polyps. Additionally, two mice sacrificed at 24 months were found to have nasal squamous cell carcinomas (*80*).

two were papillomas. No nasal tumors were found in 100 control rats. Both dosed and control rats had pneumonia but the lesions were more severe in dosed rats. The estimated bis(chloromethyl) ether (BCME) level in the exposure chamber (developing as a result of the chemical interaction of formaldehyde and hydrogen chloride) was 1 ppb. This value was computed on the basis of 10 measurements made in the mixing chamber during the course of the study. It is not certain whether the high nasal cancer incidence is a result of the formaldehyde exposure, the (presumed) BCME exposure, or the biological interaction of the two or three components of the gas mixture. Based on their previous studies (*83*), the authors considered the BCME level to be too low to be a significant etiological factor for the nasal cancers observed in this study. They also point to the fact that in rats, BCME caused mostly esthesioneuroepitheliomas rather than squamous carcinomas in the nasal cavities. While the results suggest that formaldehyde (rather than BCME) is the major etiological agent in this experiment, considerable uncertainty remains and other interpretations are possible. The authors' comparison of 20 exposure days at 100 ppb of BCME (*83*) with 500 exposure days at 1 ppb of BCME (*82*) does not, however, resolve the uncertainty of comparing the different factors involved in dose-rate versus total delivered dose in tumor induction.

Three other chronic inhalation studies with formaldehyde designed to investigate possible cocarcinogenic effects of this agent in the upper and lower airways have been reported (*84-86*). Since the nasal tissues were not systematically examined histologically, the value of these studies in assessing the carcinogenicity of formaldehyde is accordingly limited. In spite of these reservations, the studies have some bearing on the problem of formaldehyde carcinogenicity. In the studies conducted at the Oak Ridge National Laboratory (ORNL) by Nettesheim and colleagues (*84*), Syrian Golden hamsters were exposed by intratracheal (ITr) instillation to different doses of benz(a)pyrene (BaP) and by inhalation to various concentrations of formaldehyde (acrolein exposures were carried out in parallel studies). Two types of formaldehyde exposure schedules were used: 10 ppm for 5 hr/day, 5 days/week for life (two groups) and 20 or 50 ppm for 5 hr/day, 1 day/week for 17 weeks (seven groups). In all, nine groups of 88 hamsters each were exposed to formaldehyde (with or without BaP exposures; two groups were exposed to formaldehyde only). Significant in the context of this discussion is that no macroscopically recognizable nasal tumors were observed in hamsters, whereas in the studies with rats by Swenberg et al. (*79*) and by Laskin et al. (*82*), grossly visible tumors developed. Based on extensive
histopathological evaluation, there was no evidence for the carcinogenicity or cocarcinogenicity of formaldehyde for the larynx, trachea and lower airways. No neoplasms were found in two sections of nose from each hamster, but the level of sectioning was not rigorously controlled.

In the study reported by Horton et al. (*85*), C3H mice were exposed to coal tar aerosol and/or to formaldehyde at concentrations of 40, 80 and 160 ppm. Exposures were carried out for 1 hr/day, 3 days/week for 35 weeks, except for the 160 ppm group which was exposed only for 4 weeks because of toxicity. Only 15 mice survived to 1 year. There is no mention of histopathological evaluation of nasal tissues, so presumably no grossly visible tumors were observed. Coal tar aerosol exposure resulted in lung tumor formation in five animals (one invasive carcinoma) but formaldehyde exposure did not. No evidence was found for any cocarcinogenic effects of formaldehyde. The major shortcomings of this study for evaluating the carcinogenic activity of formaldehyde are that too few animals survived past one year, the individual exposures were short, most groups were exposed only for 35 weeks, and histopathology was inadequately reported.

A third study (as yet unpublished) has been performed by Dalbey and Nettesheim at the Oak Ridge National Laboratory (*86*). In this study, male Syrian Golden hamsters were exposed to diethylnitrosamine (DEN) subcutaneously (0.5 mg once weekly for 10 weeks) and to inhalation of either nitrogen dioxide (10 ppm) or formaldehyde (30 ppm). Exposures to $NO_2$ and formaldehyde were made once weekly for 48 hr prior to each DEN injection and were subsequently continued for lifetime after DEN injections were completed. An analysis of tumor data indicated that formaldehyde (but not nitrogen dioxide) might act as a tumor "enhancing agent" in the trachea as measured by multiplicity of tumors. This study was limited because, at the doses used, DEN alone produced tumors in a high proportion of animals.

The carcinogenicity of formaldehyde has also been tested by a variety of other routes of administration including subcutaneous injection (in rats), ingestion (by mice and rats), uterine cervical application (in mice) and application to the buccal mucosa (in rabbits). Because of shortcomings in experimental protocols, none of these studies permits firm conclusions regarding formaldehyde carcinogenicity. Nonetheless, some of the studies give definite clues that formaldehyde may be carcinogenic to a variety of target tissues as well as a variety of animal species (and not only to the nasal epithelium of rats).

The most revealing study in this regard is that by Mueller et al. (*87*), who applied a solution of 3% formalin to the oral mucosa of rabbits, using an "oral tank." Each exposure lasted for 90 min and was repeated five times per week for a period of 10 months. As a result, two out of six rabbits developed grossly visible leukoplakias that, according to the authors, showed histological features of carcinoma *in situ*. Unfortunately, the information given on the histomorphology of the lesions is very scanty. Nevertheless, the reported observations appear to be consistent with the rat inhalation studies, suggesting that formaldehyde is a carcinogen.

Also of considerable significance are the observations reported by Brusick et al. (*88*) concerning the transformation of mouse Balb 3T3 cells *in vitro* by formaldehyde concentrations as low as 0.5 μg/ml culture fluid. At this time no other pertinent information is available on these studies.

Probably the earliest experiments which suggest that formaldehyde is a carcinogen are those by Watanabe et al. (*89*, *90*), who injected rats (strain unknown) subcutaneously with 0.4% formalin (1 ml/week for 15 months) (*89*) and with 9-40% of hexamethylenetetramine (HMT) (from which formaldehyde is liberated *in vivo*) 1-2 ml per week until tumor development (*90*). In the first study (*89*), four of ten rats developed sarcomas at the site of the injection, and in the second study (*90*), eight out of 20 rats developed tumors, seven sarcomas and one adenoma. There is little doubt that tumors were induced by the subcutaneous injections of both chemicals over many months. It is not certain, however, what the role of the repeated severe injury to the subcutaneous tissue may have been in the induction of the sarcomas even through results with formic acid were negative (*90*).

Several other studies carried out with HMT resulted in negative findings. Brendel (*91*) administered HMT daily by gavage to 15 male and 15 female BD rats (0.4 g/day) for 333 days. No treatment-related tumors were observed. Della Porta et al. (*92*) administered HMT in the drinking water to CTM, SWR and C3Hf mice (1.25-12.5 g/kg body weight/day for up to 60 weeks) and to Wistar rats (1.5-2.5 g/kg body weight/day for 104 weeks). No treatment-related tumors were observed. Also negative was a subsequent study in which Wistar rats were given 2% HMT in the drinking water over three consecutive generations (*44*). No evidence for transplacental carcinogenicity was found. It seems clear that, in contrast to long term repeated subcutaneous administration in rats, chronic ingestion of HMT was not carcinogenic to rats and mice. A study by Klenitzky (*93*) in which "formol oil" was applied 50 times to the cervix uteri of mice (strain unknown) resulted in no tumors. It is difficult to interpret this experiment, however, because no information is available on the nature of the material used or on the quantities applied.

## Discussion of Laboratory Findings

At present only one study unequivocally demonstrates the carcinogenicity of formaldehyde. This is the study by Swenberg et al. (*79*) which showed a nasal tumor incidence of 20% in rats killed after 18 months exposure to 15 ppm of formaldehyde vapors (the cumulative cancer incidence in the 24-month exposure study is presently not known). No exposure-related tumors have as yet been found in mice which were simultaneously exposed to the same concentrations of formaldehyde. In order to clarify the significance and validity of the CIIT study which, so far at least, appears to be unique in its clear demonstration of formaldehyde carcinogenicity, we will discuss a series of questions which it raises.

(1) Is there any other evidence supporting the results obtained by Swenberg et al. (*79*)? The answer is yes. In the study reported by Laskin et al. (*82*), rats exposed to formaldehyde, hydrogen chloride, and BCME developed nasal squamous cell carcinomas. There is reason to believe that formaldehyde was a major, if not the only, etiological factor (see above). There is evidence that both formalin and HMT (which releases formaldehyde *in vivo*) cause sarcomas in rats when injected repeatedly over long periods of time (*89*, *90*). It has been reported that exposure of the oral mucosa of rabbits to formalin causes advanced preneoplastic lesions (carcinoma *in situ*) (*87*). Formaldehyde has been reported to cause transformation *in vitro* in a mammalian cell line (*88*). Formaldehyde has been shown to be genotoxic in many different test systems (see section on formaldehyde mutagenesis). A closely related aldehyde, namely acetaldehyde, was recently reported to cause nasal cancers (5%) and laryngeal cancers (14%) in hamsters chronically exposed by inhalation to 1650-2500 ppm for 52 weeks (7 hr/day, 5 days/week) (*94*).

(2) Is the carcinogenicity of formaldehyde restricted to only one species, the rat, and only one tissue, the nasal mucosa? Several references cited above suggest that it is not. Species other than rats and tissues other than nasal epithelium seem to be susceptible to the carcinogenic activity of formaldehyde. However, considerable differences in degree of susceptibility may indeed exist. Lesions interpreted to be carcinomas *in situ* were induced in the oral mucosa of rabbits (*87*). Sarcomas were produced by repeated SC injections of formaldehyde

and HMT into rats for many months (*89, 90*). Neoplastic transformation of mouse Balb/3T3 cells in culture has been demonstrated (*88*). Chronic inhalation of the closely related short chain aliphatic aldehyde, acetaldehyde, has been reported to cause not only nasal but also laryngeal carcinomas in hamsters (*94*).

The nature of the differences in species susceptibility is not clear (such differences exist, however, with almost all carcinogens); they could arise at various levels of organization (physiological, defense mechanism, pharmacokinetics, metabolism, repair capacities). An interesting parallel is the relative resistance of hamsters to BCME as compared to rats (*83*).

(3) Why is the nasal mucosa seemingly the only target tissue in rats for the carcinogenicity of inhaled formaldehyde? Nasal mucosa is directly exposed to formaldehyde and may receive the highest dose although differences in tissue sensitivity and metabolism might also be involved. It should be mentioned that formaldehyde is not the only chemical carcinogen affecting the nasal mucosa. Other carcinogens, in addition to BCME, (including systemic ones) also cause nasal tumors of susceptible hosts, for example, various nitrosamines as well as dioxane and ethylene dibromide (*95*). The experimental induction of nasal tumors in laboratory animals is thus not a rarity and does not necessarily involve direct contact, through inhalation, with the nasal mucosa of the test compound.

(4) Is the viral infection which was noted in the CIIT study likely to be a significant factor in the nasal tumor development of the formaldehyde exposed animals? The possibility that the infection (presumably caused by a corona virus) contributed to the carcinoma response in this study cannot be discounted, but the panel considered it unlikely, because the signs of infection occurred during a very short portion of the experiment (at most a week) and the first detected nasal tumors had probably already formed at the time of the infection. Although the outbreak of sialodacryoadenitis introduced an uncontrolled variable into the experiment, it is unlikely that the transient viral infection affected the outcome of the experiment. It is important to consider that people exposed to formaldehyde may also experience viral infections of the upper respiratory tract.

(5) Are the irritant effects of formaldehyde likely to contribute to its carcinogenicity? "Irritation" is a poorly defined term. As Berenblum pointed out long ago, this term is "a vague generalization representing many different kinds of injury or stimulation of the tissues" (*96*). A more specific effect that has been included under the generic term of "irritation" is the induction of epithelial hyperplasia. Many studies on this topic estimate the degree of irritation by the level of hyperplasia induced in target tissues. The role of irritation in carcinogenesis has been investigated since the early years of chemical carcinogenesis research (*96*).

More recent studies have provided evidence on the hyperplastic effects of several agents, and in some cases have provided qualitative and quantitative analyses of the tissue response. A number of agents were reported to induce epithelial hyperplasia in several types of tissues but they had no carcinogenic or tumor-promoting activity associated with them (*97-99*). The panel found no evidence that the induction of irritation or, more specifically, of epithelial hyperplasia is a sufficient condition for the carcinogenic activity of an agent.

There is, however, suggestive evidence that some agents that produce epithelial hyperplasia may play a role in the process of tumor promotion. It was found that previously initiated mouse skin exposed to a promoting agent for only a short time will develop a low level of tumor response. A high incidence of tumors may develop, however, when the short period of exposure to the promoting agent is in turn followed by exposure to an otherwise inactive irritant such as turpentine (*100*) or wounding (*101*). Repeated mechanical skin abrasion was recently found to have a promoting effect on mouse epidermis (*102*). It is therefore conceivable that the "irritant" effect of formaldehyde, or more specifically its induction of epithelial hyperplasia, may contribute to some extent to the expression of its carcinogenic activity through a mechanism enhancing the promoting or tumor growth stage of carcinogenesis. However, it must be added that our knowledge of this type of effect is still quite inadequate and not directly applicable to the reported carcinogenic effects of formaldehyde on the nasal mucosa.

(6) Are the cytotoxic effects of formaldehyde likely to be an important aspect of its carcinogenic activity? Most carcinogens have significant cytotoxic effects. Therefore, formaldehyde is not an unusual case. There are many reasons why cytotoxic agents which cause cell death and regenerative cell replication might enhance the carcinogenesis process: they increase the number of cells undergoing DNA synthesis [it is known that cells are particularly susceptible to malignant transformation prior to DNA synthesis at the onset of the DNA-synthesis phase of the cell cycle (*103*); they may force the carcinogen exposed target cells through the several cell divisions that seem to be required for "fixation" of the mutagenic or carcinogenic event (*104*); they may create selection pressures in tissues containing initiated cells favoring their proliferation and prop-

agation (*105*); and they may act as tumor promoters (*106*). In short, it is conceivable that the cytotoxic effects of formaldehyde may play a part in its overall carcinogenicity.

### Conclusions

In assessing the current evidence for the carcinogenicity of formaldehyde in animals provided by the limited number of studies conducted to date, the panel comes to the following conclusions: (1) The CIIT study provides adequate evidence that inhalation of formaldehyde vapors causes nasal carcinomas in rats. (2) There is suggestive evidence that formaldehyde might be carcinogenic in other species and tissues other than nasal. (3) Formaldehyde should be presumed to pose a carcinogenic risk to humans.

### Recommendations for Future Research

The following are recommendations for future research on the carcinogenicity of formaldehyde: (1) the pharmacokinetics of formaldehyde and its interaction with target tissue should be studied in several animal species; (2) studies of formaldehyde by other routes of administration (oral and dermal) should be initiated; (3) additional studies of neoplastic transformation of mammalian cells in culture are needed.

## Epidemiology

### Strengths and Weaknesses of Epidemiologic Methods

Epidemiologic methods for etiologic studies are designed to uncover disease and exposure relationships in human populations wherein the study groups cannot be experimentally manipulated. Individual studies must be evaluated in terms of the strengths and weaknesses of the study design, the summation of epidemiologic evidence from a variety of studies, however, requires different standards. Circumstances that allow an exposure associated with a disease to be judged a cause of the disease have been best described by Hill (*107*). First is the strength of the association. Second is the consistency of the observation. The evidence for causality is more persuasive when the association has been repeatedly observed under various circumstances by independent investigators using different methods. Third is the specificity of the association. When a specific exposure is associated with a certain disease, there is a strong argument for cause and effect. In light of multicausation of most diseases, however, the lack of specificity does not irrevocably discount a causal hypothesis. Fourth is the temporal relationship of the exposure and disease. Cross-sectional and case control studies are poorly equipped to settle this issue. Fifth is evidence of a dose-response gradient. Sixth is the plausibility and coherence of the hypothesis. The hypothesis should not conflict with generally accepted medical theory.

Completed, ongoing, and proposed epidemiologic studies discussed in this report must be individually evaluated according to the strengths and weaknesses of their design. Conclusions regarding an etiologic role for formaldehyde in disease processes must be drawn while considering findings against Hill's (*107*) points.

### Review of Completed Studies

Information on acute and chronic health effects of formaldehyde in humans comes largely from the following two sources: case reports of individuals who were exposed to formaldehyde and cross-sectional studies in which measurements of cause (formaldehyde exposure) and effect (prevalence of symptoms, signs, and disease) were made at the same point in time. In addition, limited information is available from cohort and case-control studies in which the ascertainment of cause and effect relate to two different points in time.

In this report, the assignment of published studies into the above categories was made mainly to facilitate discussion on problems and strengths associated with each category. For the purpose of this report, acute effects were defined as those that develop rapidly after a single exposure, while chronic effects were considered those that do not become manifest immediately after exposure and that persist over a period of time. The acute health effects of formaldehyde have been well documented elsewhere (*108-110*). Therefore, individual studies reporting acute health effects of formaldehyde were not reviewed in detail.

### Case Reports

Numerous case reports of health effects, presumably due to formaldehyde, are available. Contact urticaria was described in a 28-year-old woman who worked as a carver and model setter in a factory that made leather dresses containing small amounts of formaldehyde (*111*). She had urticaria almost daily, (severely on the hands, with occasional edema of the lips) during work days. During weekends and vacations, when she had no contact with the leather, there was no evidence of the skin erruption. Similarly, Harris (*112*) described four persons who developed acute papulovesicular eczema following contact with urea-formaldehyde resins. The condition persisted until the workers were reassigned to areas without formaldehyde.

Sakula (*113*) reported a case of acute respiratory distress in a hospital laboratory technician following exposure to formalin. Severe bronchial asthma followed the slightest inhalation of formalin vapor, but the worker was free from attacks on weekends and holidays. A case of pneumonitis following heavy exposure to formaldehyde by inhalation has been reported (*114*). The case involved a 27-year-old neurology resident who spent 15 hr exposed to a high concentration of formaldehyde vapor during preparation of brain specimens for student demonstrations. The following week, after only 2 hr spent at the same activity, he developed acute respiratory distress including progressive dyspnea and chest tightness over a period of 15 hr. Chest x-ray showed increased interstitial markings with early edema. A decreased pulmonary function as measured by FVC, $FEV_{1.0}$ and MMEF was also noted on day 2 and day 24 after the onset of symptoms.[*] This is said to be the first report describing a clinical picture of acute pneumonitis in man following formalin inhalation.

## Cross-Sectional Studies

***Acute Effects.*** Most of the information on the acute health effects of formaldehyde comes from cross-sectional studies of workers, volunteers, and residents exposed to formaldehyde. Symptoms associated with formaldehyde exposure include eye, nose, and throat irritation leading to lacrimation, sneezing, shortness of breath, sleeplessness, tight chest, nausea, and excess phlegm (*115-121*). An outbreak of hemolytic anemia among patients on hemodialysis was described in a recent report (*122*). The outbreak occurred shortly after a new system using filters impregnated with formaldehyde resins was installed. When the filters were removed, hematocrit values returned to previous levels. The severity and incidence of some responses were related to the concentration of exposure. In addition, the extent of reported discomfort appeared dependent on the relative humidity and temperature of the ambient air (*115, 117, 123*).

At 0.1-3 ppm, most people experience an irritation of the eyes, nose, and throat (*115, 117, 123*). Effects of exposures at higher levels are not clear; with increasing concentration, however, the discomfort increases rapidly and many people can tolerate exposures of 4 to 5 ppm for only 10-30 min (*124*). Between 10 and 20 ppm, symptoms are severe, and it becomes difficult to take a normal breath. Exposures at 50-100 ppm and above may cause serious injury to the respiratory tract, such as pulmonary edema and pneumonitis (*124*).

***Chronic Health Effects.*** Chronic health effects attributed to formaldehyde from cross-sectional studies include respiratory problems, dermatitis, neurologic difficulties, and menstrual and reproductive disorders. Schoenberg and Mitchell (*120*) studied five groups of employees from a filter-manufacturing plant to determine adverse effects of exposure to phenolic (phenol-formaldehyde) resin fumes. Groups currently exposed to phenolic resins showed an excess of chronic cough and/or phlegm when compared to previously exposed or "never-on-line" groups. In addition, after adjustments were made for differences in total cigarette consumption, workers on the present production line more than five years had a significantly lower $FEV_{1.0}$/FVC and MEF 50%/FVC ratio ($p \leq 0.05$) than the "never-on-line" group. These results suggest that long term exposure to phenol-formaldehyde resin fumes may lead to chronic airway obstruction. No systematic measurement of formaldehyde concentration was made during this study but, based on measurements by others, levels were estimated to be in the range of 0.4 to 0.8 ppm. Exceptionally high levels (8.8 to 13.5 ppm) occasionally occurred when cross-current fans were turned off during part of the sampling period. In this study every control subject was occasionally exposed to resin fumes, which may explain the high prevalence of acute symptoms such as eye irritation (80%), nose irritation (53%), and lower respiratory tract symptoms (47%) among "never-on-line" workers. Shift studies suggested a small reduction in lung function in the production line workers, whereas control workers showed a small increase. As noted by the authors, the limitations of this study include small numbers of exposed subjects, probable formaldehyde exposure among some controls, and the potential for selective bias commonly associated with cross-sectional studies. In addition, the possible role of the parent resins, phenol, and other exposure from the industrial process, such as acrylic fiber break-down products, prevents a clear determination that long-term exposure to formaldehyde may lead to chronic airway obstruction.

In a study of rubber workers exposed to hexamethylenetetramine-resorcinol (HR) resins, Gamble et al. (*125*) found more self-reported symptoms

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[*] FVC = forced vital capacity, $FEV_{1.0}$ = one-second forced expiratory volume, MMEF = maximal mid-expiratory flow rate, same as mean forced expiratory flow during the middle half of the FVC (FEF 25-75%).

(itch, rash, cough, chest tightness, burning eyes, running nose, and persistent cough and phlegm) among HR-exposed than among nonexposed workers. Contrary to the previous findings (*120*), there were no differences in lung function at baseline among exposure groups. There were, however, significant differences in lung function measurements before and after the regular work shift for HR exposed workers, but not among the non-exposed. The resin investigated in this study used resorcinol as the phenol donor and hexamethylenetetramine (HMTA) as both a formaldehyde donor and a catalyst. There was no association between lung function and ambient levels of resorcinol, formaldehyde, hydrogen cyanide or ammonia. Mean concentrations of formaldehyde were 0.05, 0.02 and 0.04 ppm for HR-exposed, HR-not exposed, and control group, respectively. Decrease in pulmonary function was related to the quantity of respirable particulates obtained from personal samples. Chemical analysis of particulates, however, was not performed. It is unlikely that formaldehyde by itself was responsible for the change in pulmonary function for two reasons: (1) the exposure level of formaldehyde was very low and (2) no association between its level and decrease in pulmonary function was observed.

Eight cases of occupational asthma (three smokers and five nonsmokers) were reported among 28 members of the nursing staff at a hemodialysis unit where formalin was used to sterilize the artificial kidney machine (*125*). Recurrent episodes of productive cough accompanied by wheeze were a prominent feature and, for five persons, attacks had extended over the previous three years. Inhalation provocation tests were performed on five subjects with histories of recurrent attacks of wheezing. In two of these subjects the test resulted in asthmatic attacks like those experienced at work. Peak expiratory flow rates fell approximately 50% and wheezing began 2 and 3 hr after exposure to formalin and lasted for 10 hr to 10 days. Three of the five subjects had no respiratory reaction to inhalation of formaldehyde similar to that experienced in the dialysis unit. Two of the five had no symptoms, while one developed conjunctivitis. This latter patient developed redness, weeping and sensations of grittiness of the eyes when heavily exposed to formalin. In the absence of symptoms and exposure there was no apparent reduction in lung function. The authors suggest that although formalin may not have been the etiologic agent in all cases, it may have increased the susceptibility to other agents, which could, perhaps, explain the high incidence of bronchitis-like symptoms. In the absence of a comparison group, an alternative explanation of the asthma being attributable to chance alone still exists. However, the explanation is unlikely because of the high proportion of the staff which developed the symptoms and because of the positive responses observed after the inhalation provocation test.

Formaldehyde-related asthma and dermatitis were also reported by Kerfoot and Mooney (*121*). A survey of six Detroit area funeral homes showed that embalmers were generally exposed to formaldehyde at mean levels ranging from 0.25 to 1.39 ppm with a total range of 0.09-5.26 ppm. They experienced acute toxic effects including eye and nose burning, sneezing, coughing, and headaches. Asthma or sinus problems were reported by 3 out of 7 morticians. In addition, two workers experienced dermatitis, with one case being so severe that he discontinued working for a period of time until he recovered. Although it was the professed intention of the authors to correlate the formaldehyde concentrations in each funeral home with the irritant effects on embalmers who worked at the particular funeral home, no data were presented to that end in this study. A dosage effect was implied in the sentence, "The morticians who spent more time embalming than in general funeral work, also experienced more complaints of irritations." It was not clear who and how many people were in the study. Embalming agents contain formaldehyde as well as a variety of other chemicals, such as tissue moisturizers, smooth muscle relaxants, bleaches, an auxiliary antiseptic agent (phenol), dyes, buffers, wetting agents, water conditioners and/or anticoagulants, perfumes and odor suppressors, and vehicles (methanol, ethanol, and glycerine). In light of the possible mixed exposure to a variety of the above chemicals during embalming and the lack of an appropriate control group in the study, the relationship of formaldehyde exposure among embalmers to development of asthma and dermatitis remains inconclusive.

Yefremov (*127*) studied 278 workers at two wood-processing plants where urea-formaldehyde resins were used extensively. They reported that the incidence of chronic diseases affecting the upper respiratory tract was higher in workers exposed to formaldehyde than in a control group consisting of 200 individuals of corresponding ages. The prevalence was from 28.1 to 58.3% depending on work areas, among formaldehyde-exposed workers, compared to 13% among the controls. The highest prevalence of disease (58%) was observed in the workers at the hot press shop, where the concentration of formaldehyde was 2.5 times that in the cold press shop. Disease occurrence was 33.9% at the cold press shop. In all work areas the formaldehyde concentrations were reportedly below the maximum permissible concentration (0.4 ppm). Assuming the age-matched controls represent an appropriate comparison group (no mention was made of matching on sex and smoking history), this report supports the hypothesis that exposure to formaldehyde may lead to chronic respiratory diseases.

Kratochvil (*128*) examined a total of 18 workers of a mean age of 35 with an average formaldehyde exposure of 7 years in a clothing production plant. Formaldehyde exposure occurred during storage and processing of fabric impregnated with urea-formaldehyde and melamine-formaldehyde resins. Catarrhal conjunctivitis was found in 72% of the workers; 28% of the workers exhibited a catarrhal inflammation of the upper respiratory tract, 22% of the workers exhibited chronic bronchitis diagnosed in accordance with the criteria of the World Health Organization, and 11% of the workers showed skin changes. Lung function tests showed that the vital capacity and the differential forced vital capacity exhibited normal values for all workers. The concentrations of formaldehyde in these work areas were below the maximum allowable concentration (0.4 ppm). In the absence of an appropriate control group, an etiologic role of formaldehyde in development of the above conditions is uncertain. In fact, the 22% incidence of chronic bronchitis among the workers corresponded to the incidence of this condition reported for a normal population of a similar age group.

Shumilina (*129*) reported a high incidence of menstrual and reproductive function disorders among 446 women workers (130 finishers and 316 inspectors) exposed to urea-formaldehyde resins. Formaldehyde concentrations of 1.2 to 3.6 ppm were often found in the finishers' work area of the fabric trim shop, while levels from 0.04 to 0.56 ppm occurred in the inspectors' work area. A group of 200 saleswomen not exposed to formaldehyde was used for comparison. The reproductive disorders reported to be more common among those exposed included menstrual disorders, increased complication during pregnancy, and higher percentage of neonates with low birth weights. The role of formaldehyde in the development of these disorders is uncertain, however, because of the lack of information on the work environment and the socioeconomic status of the study and control groups. In addition, many of these disorders are known to be associated with physical and mental stress, personal habits (alcohol, cigarettes, caffeine consumption), nutritional status, and other factors related to the socioeconomic status of women. Still, these findings are intriguing and indicate a need for further studies in this area.

Neshkov and Nosko (*130*) reported a high incidence of sexual dysfunction among male workers employed in a plant producing glass fiber reinforced plastic. These workers were exposed to vapors of phenol, formaldehyde, aniline, epichlorohydrin, diphenylpropyl, styrene and a combination of glass fiber and glass-reinforced plastic dust. The levels of each of these chemicals were 1.5 times the respective maximum permissible level in 63% of the samples (maximum permissible level of formaldehyde is believed to be 0.5 $mg/m^3$ or 0.4 ppm). Among the 143 workers examined, 58 (40.5%) had psychoneurologic and sexual complaints. Sexual complaints included a diminution of libido, premature ejaculation, a weakening erection and decrease in the satisfaction derived from an orgasm. Analysis of the sexual complaints revealed a direct relationship to the duration of employment at the plant. Testicular dysfunction among the workers was also reported, including decreased volume and increased viscosity of ejaculate and decreased number of spermatozoids. The authors concluded that these sexual dysfunctions were the results of complex toxic effects of chemicals on the cells of the cortex and those of the subcortical brain stem structures, which participate in the regulation of sexual function. It is impossible to determine how much of the sexual dysfunction might be attributable to formaldehyde since appropriate control groups were not included and these workers were exposed to a variety of toxic chemicals in addition to formaldehyde. Of particular interest are reports of epichlorohydrin-induced sterility in animals (*131*, *132*).

Ishchenko and Pushkina (*133*) compared morbidity and sick leave among 662 workers engaged in the manufacture of phenol-formaldehyde resins to that among 473 unexposed workers. Several disease conditions were more common in the formaldehyde exposed group than in the controls, particularly from diseases of the respiratory tract (1.8-fold among males and 1.4-fold among females). Among women, the frequency of urogenital problems was 2.3 times more common in the exposure group. Days absent from work due to illness among those exposed exceeded controls 1.5- to 1.6-fold. Although the authors state that the age distribution of the exposed and comparison populations was similar, no description of the methods used to determine morbidity (examination, self-report, or medical records) was provided. In addition, uncontrolled social factors, as recognized by the authors, may play a role. In light of these limitations, the greater number of lost workdays due to sickness and the increased evidence of respiratory and urogenital diseases among the exposed workers, although suggestive, does not provide definitive evidence concerning the role of formaldehyde.

In a mail survey of 20 funeral homes in Los Angeles (*134*), 57 of 80 embalmers responded. Nine (16%) reported symptoms compatible with acute bronchitis and 17 (30%) were considered to have chronic bronchitis. The 31 asymptomatics, however, had worked longer than the bronchitics (18 years vs. 11 years). In the absence of a control group, these findings are, at best, suggestive.

Engel and Calnan (*135*) reported an outbreak of dermatitis in a car factory. A total of 50 cases of dermatitis were observed in three years (1962-1965) among 150 employees who handled rubber weather strips coated with phenol-formaldehyde resins. The workers who developed dermatitis had been exposed to the adhesives containing phenol-formaldehyde resins for from one day to two years before the onset of the eruption, with an average period of contact of 17 weeks. The average duration of the eruption was 12 weeks, however, in three cases it persisted up to 2½ years. The eruption was generally an erythematous vesicular rash of the fingers and hands. Three materials were handled by these employees: (1) the rubber weatherstrips, used for some years; (2) adhesive A and B introduced 4 years before in 1962 and supplied by the same manufacturers; (3) toluene, which was the solvent used to activate the adhesive. The rubber weatherstrips alone were ruled out as a cause because they came from various suppliers and had not changed in composition for a long time. The toluene would not be expected to cause sensitization within a short period of time. Among the 29 patch-tested dermatitis patients, four (14%) gave a weak reaction to phenol alone, while 65% had a positive reaction to the adhesive resins. It is, therefore, probable that formaldehyde in the resins was a causal agent. Outbreaks of dermatitis in several industries using formaldehyde resins were reported by Schwartz, Peck and Dunn (*136*). In a factory where plywood was laminated, 600 cases of dermatitis were reported among about 800 workers during the first six months of operation. In a second reported outbreak, over 40 workers out of a total of 100, developed dermatitis in a factory making tool handles from laminated glass fabric and phenol-formaldehyde resins. Although no unexposed group was available for comparison, the high proportion of formaldehyde exposed workers developing dermatitis is quite impressive.

In a hemodialysis unit where formalin was used as a sterilant, 6 to 13 staff members developed dermatitis within 3 weeks (*137*). Four of the six were positive in patch tests with 3% formalin. It was not clear why only the hemodialysis unit was affected, since other units also used formalin. The author speculated it might be due to the use of a detergent that lowered the resistance of the skin to formaldehyde vapors and to the high temperature and concentration of formalin in the preparation room. Lack of controls hampers the interpretation of these data.

## Cohort and Case-Control Studies

The panel was not aware of any published cohort of case-control studies designed to evaluate the role of formaldehyde in the development of disease or abnormal conditions. Many mortality studies have been reported of workers from occupations or industries wherein formaldehyde exposure may have occurred. For example, Moss and Lee (*138*) have reported elevated risks of oral and pharyngeal cancer among male textile workers. They reported 77% excess deaths due to these cancers compared with the male population of Wales and England. These textile workers may have been exposed to formaldehyde, since formaldehyde has been widely used in the textile industry for producing creaseproof, crushproof, and shrinkproof fabrics. No environmental measurements of formaldehyde, however, were made in this study. A recent NIOSH survey showed concentrations of formaldehyde in the textile plants in the U.S. ranging from 0.1 to 1.4 ppm.

Bross et al. (*139*) reported a significantly increased risk of nasal cancer among brickmasons, textile workers and shoemakers. Textile workers also had significantly elevated risk of cancer of the pancreas and stomach. No information on formaldehyde concentrations was reported.

Decoufle (*140*) has reported significantly increased risks of cancer of the buccal cavity, pharynx and larynx among male leather workers. Bladder cancer and malignant lymphomas were also associated with increased risks among male and female employees in the leather industry. The cancer risk for the employees was calculated relative to the risk for those who were in clerical positions. A variety of chemicals including formaldehyde, azo dyes, chromium compounds and tanning extracts have been used in the production of leather goods. Some of these chemicals are carcinogenic in animals. Industrial hygiene surveys of a calf skin tannery in the U.S. showed concentrations of formaldehyde in the finishing department ranging from 1 to 8.6 ppm (*141*).

Matanoski (*142*) reported an excess of primary liver cancer and lung cancer among pathologists compared to radiologists. However, oral and pharyngeal cancers were lower in the pathology group. Although exposure estimates were not available, pathologists are more likely than radiologists to be exposed to formaldehyde.

Although the above investigations were not designed to study health effects of formaldehyde, the results suggest the possibility of formaldehyde being carcinogenic in humans. The lack of precise information concerning the number of persons exposed to formaldehyde and the level of exposure, in addition to the problems of confounding exposures, makes interpretation of these reports regarding formaldehyde difficult.

## Conclusions

In summary, a wide variety of acute and chronic health effects from formaldehyde exposure have been reported. They include eye, nose and throat irritation, headache; shortness of breath; wheezing; dermatitis; chronic cough; excess phlegm; chronic airway obstruction; asthma; bronchitis; rhinitis; pharyngitis; menstrual and reproductive disorders; sexual dysfunction; and possibly cancer. These studies were primarily of a cross-sectional design, thus, they do not allow a clear determination of the order of events. In addition, many studies lacked appropriate controls and/or environmental measurement, making it difficult to clearly evaluate the role of formaldehyde. Independent reports of respiratory system disorders and dermatitis among persons from a variety of work settings supply evidence on the consistency of the association, and indicate that formaldehyde is a likely contributor to the origin of these diseases. Only three studies (*120*, *125*, *127*) allowed an estimate of the strength of association between formaldehyde and respiratory disease. The risk of chronic respiratory symptoms among exposed groups ranged from about 1.5 to 4.5 times that among nonexposed groups, with little evidence of a dose gradient. The studies of dermatitis among workers exposed to formaldehyde, although reporting a high prevalence, lacked comparison populations necessary to estimate the strength of the association. Respiratory and integumentary systems are plausible response sites since workplace exposure to formaldehyde is likely to occur by inhalation or dermal contact.

The report of excessive menstrual and reproductive problems among women exposed to formaldehyde is provocative and, despite the study limitations, indicates the need for further research in this area. No reports of studies specifically designed to evaluate the carcinogenicity of formaldehyde in human populations were available, but several such studies are in progress.

## Review of Planned and On-Going Epidemiological Studies of Formaldehyde

Planned and on-going investigations related to formaldehyde exposure include one study of a new technique of measuring formaldehyde, three studies investigating complaints, four epidemiological studies of morbidity (cross-sectional and prospective), and six mortality studies (cohort, proportionate mortality, and case-control). The questions being addressed and an evaluation of each group of studies follows.

### Measurement Technique

The use of solid absorbent surfaces for collecting personal samples of vapor and particulate formaldehyde is being examined. This method should be more sensitive and efficient than the present impinger method, thereby permitting more accurate assessment of environmental exposures. An occupational study (cross-sectional morbidity) is planned, but details have not yet been provided.

### Investigation of Complaints Relating to Formaldehyde

The results from three states are being compiled. In Connecticut, persons complaining of health problems due to urea-formaldehyde insulation completed a questionnaire concerning their symptoms and air levels of formaldehyde were measured in their homes. Occupants 489/794 of 262 residences presented complaints, the most common symptoms being eye, nose, and throat irritation, and headaches. Formaldehyde concentrations ranged from 0 to 10 ppm (mean of 1.5 ppm). About half of the complaints were associated with levels of 0.5 to 10 ppm.

F. Marshall of the New Jersey Department of Health obtained medical histories, all available information on insulation, and patterns of health effects from residents with recently installed urea-formaldehyde foam insulation who complained of formaldehyde odor, irritation, or increased pre-existing illness patterns. In 40/55 homes investigated, the most common symptoms were tearing of the eyes, sore throat, cough, and runny nose. Air samples were collected in 22 homes. In 14 homes where formaldehyde was detected, levels ranged from 0.01 to 0.78 ppm.

In New Hampshire, the Bureau of Occupational Health (M. Hilgemeier) administered a standard questionnaire to residents with complaints associated with formaldehyde exposure. Standard NIOSH techniques were used to collect formaldehyde samples. About 90% of the samples were below 0.5 ppm; 10/77 dwellings were mobile homes.

The above studies on formaldehyde complaints are all similar and suffer the same deficiencies. None of them can be used to estimate prevalence of symptoms nor can they be used to establish dose-response relations. These shortcomings include: (1) the surveys are conducted only among those who complain, and although the prevalence of symptoms should be high, it is a biased sample; (2) there are no controls and no measurement of other irritants that could cause health complaints. Thus, these studies are only suggestive of possible problems and by themselves provide little evidence of cause and effect relationships.

## Morbidity

R. Levine of the Chemical Industry Institute of Toxicology studied approximately 100 West Virginia morticians in a cross-sectional study of lung function (spirometry) and respiratory symptoms. Employment and smoking histories were also obtained. Industrial hygiene measurements made in the mortality study of Ontario embalmers along with symptoms during embalming, number of bodies embalmed, subjective assessment of severity of fumes, and length of employment will be used to assist in the estimation of exposure in this study. Spirometry will be compared to predicted values from Knudson, and internal comparisons will be related to exposure after age, height, and smoking adjustments. Data from this study are being analyzed in terms of the prevalence of respiratory symptoms (cough, phlegm, dyspnea) and the relation of percentage of predicted pulmonary function to employment (formaldehyde exposure) after adjustment for confounding variables. There is no assessment of skin effects. It is not clear if acute symptoms related to exposure are to be evaluated. Although there is a good rationale for studying this occupational group, an inability to detect a significant response in this study could be due to low cumulative exposure (probably less than 8 hr/day). Length of exposure (years worked or latency) should be adequate. If we assume 50 persons each (smoking groups combined) in a high and low exposure group (the optimal situation) there is an 85% chance of correctly rejecting the null hypothesis of no difference in FEV between exposure groups, if the true difference is 0.5 liters and $\alpha$ level is 5%. If the symptom rate is 20% in the low exposure group, there is less than a 50% chance of correctly rejecting the hypothesis of no difference if the true difference is 20% at the 5% level (two-tailed test). As in all cross-sectional studies, estimates of exposure are only a crude indicator of actual exposure. This is, however, one of the few studies to attempt to assess long term effects of formaldehyde on lung function. Although embalming fluid contains 1-2% formaldehyde, other pulmonary irritants are also present (e.g., phenol) but these may be at low enough concentrations to have a minimal effect. A comparison group (e.g., funeral directors) would have provided more confidence in the results and more power in the analysis.

The remaining three morbidity studies are of residents in homes with urea-formaldehyde (UF) foam insulation. In the first of these, M. Thun of the New Jersey Department of Health identified about 400 homes that had been insulated with UF foam and an equal number of control homes. Information gathered by telephone interview included type of home and insulation, formaldehyde odor, health symptoms and other medical data, demographic data on the occupants, and the period prevalence of asthmatic attacks, wheezing, chest pain, stinging or burning skin, burning or tearing eyes. Except for wheezing, the controls reported a higher prevalence of symptoms than did UF foam households. There was no detectable difference in the overall incidence of new symptoms during the year. There was, however, an association of increased symptoms and formaldehyde odor; the incidence of new symptoms following installation of the insulation was 2.7 times higher than in the months preceding the insulation. About 64% of the residents of the UF foam homes reported no problems at all related to the foam insulation. There is the possibility of selective recall in the remaining 36% of the study group because of the possible publicity relating to mobile homes and the specific questions relating to insulation. Despite this potential bias, there was little overall difference between study and comparison populations. There was, however, a dose-response relation (dose was based on odor). Unfortunately, there were no environmental measurements to correlate with odor perception and symptoms, and apparently no control of other potentially confounding irritants other than formaldehyde. The added insulation may have also increased other respiratory irritants that could have raised the symptom rate. It is not clear how the formaldehyde odor was described to the subjects. This study has been completed recently and should be available for review shortly. The summary given the Panel suggests little difference between the insulated and control homes except when odor occurred.

M. Woodbury and C. Zenz of the Wisconsin Department of Health and Social Studies are proposing to study 110 new mobile home owners. Exposure measurements are to be made twice monthly for 9 months. It is difficult to evaluate this prospective study because of the lack of detail provided. Some of the questions that need answering are: What are the health parameters that will be determined and how often are they being monitored? Are there formaldehyde controls for the mobile homes? If so, how are they selected? If no controls are planned, the study will have limited value. Are other respiratory irritants being measured (e.g., $NO_2$)? About 50% of the homes are newer homes with higher formaldehyde levels than the older homes which are serving as controls and have measurable but low levels of formaldehyde. Assuming a 20% symptom rate and 180 people in each exposure group (high and low formaldehyde), there is about an 85% chance of correctly rejecting the hypothesis of no differences in symptoms when the true difference is 15% at the 5% α level, and about a 99% chance of correctly rejecting the hypothesis of no difference in $FEV_1$ when the true difference is 500 mL at the 50% α level (two-tailed test). The effects of long-term chronic exposure cannot be estimated by this study. These investigators also performed a retrospective pilot study of 65 mobile home residents. The data will be mainly useful in the planning and execution of the prospective study.

L. Williams of the Oregon Department of Disease Monitoring and Control is planning to study 300 mobile home residents who responded to a health questionnaire. The volunteers were from two regions, coastal and inland. The purpose of the study is to ascertain the effect of humidity, temperature, and wind ventilation on "health effects to potential formaldehyde exposure." Inasmuch as the participants in the study are volunteers, however, it is not a random sample. Apparently, environmental measures are planned, but it is not known what other information on insulation, demography, other pulmonary irritants, humidity, temperature, etc., will be collected. Although the details are unknown, this study design does not promise to add very much to our knowledge. The power in this study is similar to the study by Woodbury and Zenz when the following assumptions are made: (l) the two exposure groups to low and high formaldehyde are of equal size ( ~ 150); (2) the prevalence of symptoms is about 30% in low exposure group.

## Mortality

H. Weiss of the Wisconsin Department of Health and Social Sciences conducted a case-control study of infant mortality by type of residence and found an increased risk for mobile home residents. Socioeconomic status is only one of many sources of potential bias in this study. The completed study should be reviewed, but the short description available suggests that the data will provide little, if any, useful information on the effect of formaldehyde.

D. Grauman of the National Cancer Institute proposes to evaluate the mortality experience (using standardized mortality ratios [SMR] of a cohort of about 11,000 medical technologists. This group is exposed to other chemicals in addition to formaldehyde (e.g., chloroform and benzidine). No environmental data are available, so there cannot be a good estimate of exposure-response relationships. A positive association will not be conclusive because of the mixed exposure. A negative association will not be conclusive because of the lack of exposure information and the possibility of low exposures. The control group is to be the U.S. population. If 15% of the cohort are dead ($n$ = 1650 cases) and if 20% of the deaths in the control population were from cancer, there would be better than a 95% chance of correctly rejecting the hypothesis of no difference between exposed and controls if the true differences were 5% at the 5% α level. Assuming 1/4 of all cancers were lung cancer, there is about an 80% chance of correctly rejecting the hypothesis of no difference if the true differences were 5% at the 10% α level (two-tailed test).

There are three mortality studies of embalmers. J. Walrath is conducting a proportionate mortality ratio (PMR) analysis of about 1500 morticians from New York. The purpose is to determine whether there is an excess proportion of deaths due to specific malignant neoplasms compared to the general population. Besides having the problems inherent in a PMR analysis where the population-at-risk is not available there is little exposure data (length of exposure is estimated on the basis of the year first licensed). Assuming the rate of lung cancer is 5%, there is better than a 99% chance of correctly rejecting the hypothesis of no difference in lung cancer rates when the true difference is 5% at the 1% α level (two-tailed test). Walrath is also conducting another PMR study on about 1200 embalmers from California. This study is very similar to the one in New York, except there will be more information on length of exposure which can be evaluated. There is, however, no direct estimate of exposure or smoking history or other confounding exposures. If 20% of the deaths were from cancer, there would be a better than 90% chance of correctly rejecting the hypothesis of no difference in cancer rates between exposed and controls if the true differences were 5% at the 10% α level (two-tailed test). R. Levine of the Chemical Industry Institute of Toxicology is also studying embalmers using an SMR retrospective mortality design. The cohort is composed of Ontario's funeral service professionals licensed during 1914-1967. Date of birth, date of first licensure, type of license, years licensed, and place of employment are available for each person. Observed mortality rates will be compared to Canadian national and provincial mortality data. Mortality will also be analyzed as a function of exposure (years worked?). A retrospective industrial hygiene assessment will consist of inquiring about changes in funeral practices with time, surveying several selected funeral establishments. The survey will include air sampling for agents of potential health concern (e.g., formaldehyde, phenol) and examination of purchase records to determine amount and kind of chemicals used. Presumably these data are to be used in evaluating dose-response relationships. Assuming the study population comprises 180 deaths (15% of the estimated cohort) and a 20% cancer rate there is about a 50% chance of correctly rejecting the hypothesis of no difference if the true difference is 10% at 5% $\alpha$ level (or an 85% chance if the true difference is 15% at the 5% $\alpha$ level). As a group, these three studies of embalmers should provide a good estimate of potential risk from formaldehyde exposure.

A. Blair at NCI and the Formaldehyde Institute are collaborating on a proposed cohort mortality study to develop age, race, and sex-specific mortality rates among formaldehyde-exposed workers. Rates will be compared with those in the U.S. population and local or regional populations where appropriate.

The first phase of the investigation is to determine if there is a suitable cohort for study. Suitability will be based on representatives of the participating companies, range of exposure, availability of a cohort of at least 3,000 workers with a minimum 15-year latent period, suitable age distribution, and sufficient information for adequate follow-up. If the requirements for a scientifically sound study are met, the study will proceed. Formaldehyde exposure for each individual will be estimated using job titles, work locations, past environmental measurements, years of employment, and the presence of potentially confounding exposures. The exposed group will be stratified by intensity and duration of exposure, age and year of first exposure, susceptibility, and latency.

The cohort should be large enough to engender confidence in the differences in mortality experience of study and comparison populations. Although exposures are unlikely to be pure formaldehyde, because of the varied occupational exposures and size of the cohort, it may be possible to assess the individual contribution of formaldehyde. Although the assessment of exposure is retrospective, it can still be at least semiquantitative. This is a very important part of this study and should employ a full-time industrial hygienist following methods similar to those of Emsden at the University of Pittsburgh. It is important that all companies participate in the study, as the results may be seriously biased if some do not.

## Conclusions

Of all the mortality studies proposed, those examining the medical technologists, embalmers, and formaldehyde workers are the only ones that can assess the carcinogenic risk among those individuals exposed. Although single epidemiologic studies usually cannot adequately assess an occupational risk, or the risk of exposure to a chemical agent, taken together these studies should help clarify the situation. There are, however, a number of concerns about these studies.

- Are exposures to formaldehyde high enough in these populations to assess possible effects? For example, are embalmers exposed 8 hours/day, 5 days/week, or is their exposure much less?
- Can exposure history be adequately documented? Are individuals with little or no embalming experience distinguishable from those with considerable exposure? Since few if any of the workers are exposed only to formaldehyde, what is the effect of exposure to these other agents?
- Is exposure to formaldehyde in the same range as for other populations?

The confidence we place in the findings from these studies depends largely on the ability to retrospectively estimate exposure. If exposure in these occupational groups is representative of other exposed populations, the conclusions may be indicative of potential risk to all exposed populations. If these studies do not adequately address the above questions, then further investigation may be required. Such investigation may be pursued within the existing data set, or new populations may need to be investigated.

## Recommendations for Epidemiologic Research

There is a need for carefully designed epidemiologic studies to evaluate the role formaldehyde may play in the origin of certain chronic diseases. Specific research areas identified by the panel include the following: (1) additional studies of chronic respiratory system disorders that include environmental measurements to allow a more precise estimate of risk at various exposure levels, including industrial, as well as mobile home populations; (2) projects designed to confirm or deny the association of menstrual and reproductive disorders and formaldehyde exposure reported by Shumilina (*15*); (3) more complete epidemiologic studies to evaluate the carcinogenicity of formaldehyde in human populations. Although several projects are under way, there is a need to be alert for resources for additional research. The widespread use of formaldehyde in industry and its occurrence in a variety of consumer products may provide opportunities for other studies. The many uses of formaldehyde are summarized in the NIOSH Criteria Document (*108*) and will not be itemized here. It is sufficient to say that the chemical is of importance in adhesives for particle board and plywood production; resins to mold a variety of plastic parts for automobiles, appliances and hardware; wrinkle-resistance in textile manufacturing; strengthening of various paper products (grocery bags, wax paper, napkins and tissues, and filter paper); specimen preservation; mildew prevention; insulation; and protective coatings.

It may be possible to identify other formaldehyde-exposed cohorts for study. The major difficulty is that, for most occupations or industries, only a small proportion of the workers have actual contact with formaldehyde. This is clearly demonstrated from the NIOSH Occupational Hazard Survey, Phase I, 1972-1974, where 4,636 plants were studied in over 600 different industry types (according to S.I.C. codes). These plants employed 895,725 workers in 453 different occupations. Products containing formaldehyde were encountered in 396 separate S.I.C.-coded industries. Table 1 lists the percentage of workers exposed to formaldehyde in the industries with the larger work forces, and those of particular interest.

Table 1. Percentage of workers exposed to formaldehyde.

| Industry | % of workers exposed |
|---|---|
| Medical | |
| Veterinarian and animal hospitals | 23.0 |
| Funeral services | 100.0 |
| Medical laboratories | 31.9 |
| Construction | |
| Forestry services | 10.5 |
| General building contractors | 3.6 |
| Heavy construction | 3.7 |
| Plastering and lathing | 5.4 |
| Textiles | |
| Finishing plants (synthetics) | 11.6 |
| Coated fabrics | 14.0 |
| Hats and caps | 47.0 |
| Fabricated textile products | 3.3 |
| Wood and paper | |
| Veneer and plywood | 21.0 |
| Wood products | 8.6 |
| Upholstered furniture | 12.2 |
| Paper mills | 5.8 |
| Paper coating and glazes | 9.0 |
| Bags (except textiles) | 11.1 |
| Paints and allied products | 16.9 |
| Fabricated rubber products | 29.0 |
| Abrasive products | 11.0 |

This survey confirms an impression given by published reports that exposure to formaldehyde is more common in medical and laboratory environments and in certain parts of the textile, wood, and paper industries. In certain industries, however, the number of work places and workers studied was small and the survey may not have included those where significant exposure to formaldehyde occurs (e.g., the chemical manufacturing industry).

The Industry-wide Studies Branch of NIOSH is carrying out an industrial hygiene study of formaldehyde exposure in several industries in search of a suitable cohort for a mortality study of formaldehyde exposed workers. Measurements will be made in industries concerned with formaldehyde manufacture, textile and clothing production, wood furniture and wood and paper product manufacture. Fifteen site visits are planned and these will be completed over the next six months.

The major difficulty of the mortality studies of individuals exposed to formaldehyde is the limited ability of such studies to detect excess risk for rare causes of death. Since the known carcinogenic action of formaldehyde is limited to the nasal sinuses in rats, there is a need to evaluate the risk for this site in man, although it is clear that carcinogens may not affect the same tissues in humans as in laboratory animals. It is unlikely that a cohort of sufficient size can be assembled to accomplish this task; however, a carefully designed case-control study might. The panel suggests that the feasibility of performing a case-control study of cancer of the nasal sinuses in areas where there is heavy production or use of formaldehyde as a vapor should be explored.

## Evaluation of Risk

### Nasal Tumor Risk in Rats Due to Formaldehyde Inhalation

Existing data on humans exposed to formaldehyde provide no quantitative estimates of the incidence of irreversible diseases. Epidemiologic studies are in progress which may be useful in identifying and estimating chronic disease risk due to formaldehyde vapor exposures.

A study was sponsored by the Chemical Industry Institute of Toxicology to investigate the toxic effects of inhalation of formaldehyde vapor in Fisher 344 rats and B6C3F1 mice. Animals were exposed to average dosages of formaldehyde vapor of 0, 2.1, 5.6 and 14.1 ppm for 6 hr/day, 5 days/week, for 24 months. A total of 120 animals/species/sex were exposed at each dosage level. Within each group, 10 animals were sacrificed at 6 months, 10 animals at 12 months and 20 animals at 18 months. The frequency of nasal tumors in Fischer 344 rats through the 18 month sacrifice was reported by Swenberg et al. (*79*). Since no significant differences were noted in the frequency of nasal tumors between sexes during the first 18 months of exposure, the results for the sexes were combined. No nasal tumors were observed prior to 12 months. The results given are summarized in Tables 2 and 3.

Tumors in two categories were considered for risk analysis: squamous cell carcinoma and total nasal tumors. Since time-to-tumor data were not presented by the authors risk analyses are performed only on the unadjusted tumor rates of animals dying with tumors prior to 18 months. The number of unscheduled sacrifice animals at risk for the combined sexes prior to 18 months is 200 per dose.

Using a procedure given by Crump et al. (*143*), the multistage model of carcinogenesis was fit to the proportion of animals dying with tumors before 18 months. Note that this analysis does not give the probability of death due to tumors. Time-to-tumor and cause of death data are not given by Swenberg et al. (*79*): hence a competing risk analysis utilizing the sacrificed animals cannot be performed. The upper 95% confidence limits for the proportion of animals dying with squamous cell carcinomas before 18 months were 0.3, 2.0 and 17.1% for 2.1, 5.6 and 14.1 ppm, respectively. Even though no squamous cell carcinoma were observed at the two lower dosages, because of statistical uncertainty there is no guarantee that squamous cell carcinomas cannot occur at 5.6 ppm or less in Fischer 344 rats within 18 months.

Since the true form of the dose response curve below 2.1 ppm is unknown, nasal tumor rates in rats exposed below this level cannot be predicted directly. Since the dose response is curving upward (convex), the potential nasal tumor rates at lower dosages are predicted to be proportionately lower than the potential risk at 2.1 ppm. The upper confidence limit on the rate of squamous cell carcinomas is 0.3% at 2.1 ppm. At 1 ppm the risk is predicted to be at least a factor of 2.1 lower, i.e., 0.003/2.1 = 0.0014, etc. In general, proportional dose response predictions (linear extrapolation) for dosages below 2.1 ppm are given by: Squamous cell carcinoma rate ≤ 0.0014 × dosage (ppm).

Similarly, the upper 95% confidence limit for the proportion of animals dying before 18 months with

**Table 2. Frequency of nasal tumors in animals dying prior to 18 months.**

| Dosage, ppm | Number dying | Tumor frequency | | |
|---|---|---|---|---|
| | | Squamous papilloma | Squamous cell carcinoma | Spindle cell sarcoma |
| 0 | 2 | 0 | 0 | 0 |
| 2.1 | 2 | 0 | 0 | 0 |
| 5.6 | 8 | 0 | 0 | 0 |
| 14.1 | 44 | 4 | 28 | 1 |

**Table 3. Frequency of nasal tumors in animals sacrified at 18 months.**

| Dosage, ppm | Number examined | Tumor frequency | |
|---|---|---|---|
| | | Adenomatous polyp | Squamous cell carcinoma |
| 0 | 40 | 0 | 0 |
| 2.1 | 40 | 1 | 0 |
| 5.6 | 40 | 1 | 0 |
| 14.1 | 40 | 1 | 8 |

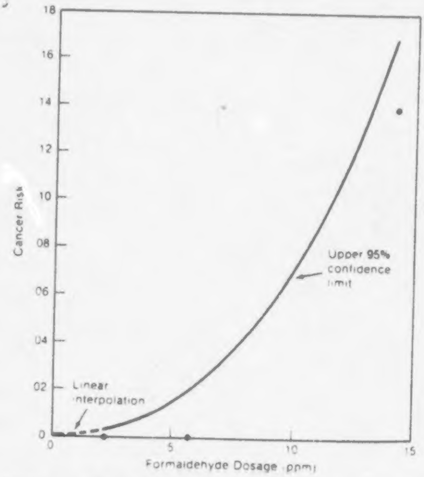

FIGURE 4. Potential proportion of Fischer 344 rats dying with squamous cell nasal carcinomas before 18 months.

any nasal tumor is 0.33%, giving: Total nasal tumor rate $\leq 0.0016 \times$ dosage (ppm). For example, the proportion of animals dying before 18 months with squamous cell carcinomas in Fischer 344 rats is predicted to be no more than 1.4 per 1000 animals at an exposure of 1 ppm formaldehyde for 6 hr/day, 5 days week. The low dose extrapolation procedure is illustrated in Figure 4.

The rat data indicates a potentially high nasal tumor rate at inhalation exposure levels comparable to levels which can be experienced in homes and occupational environments. Perhaps the epidemiology studies in progress will provide direct tumor risk information for humans exposed to formaldehyde.

## Conclusions

The metabolic pathways for formaldehyde in various animals species and man are qualitatively the same but differ in rate with formaldehyde or a formaldehyde adduct likely to be the carcinogenic agent.

Most of the studies available on the possible teratogenicity or reproductive effects of formaldehyde are inadequate for evaluation and none are adequate for exposure by inhalation.

Formaldehyde is mutagenic in a variety of test systems, including bacteria, yeasts, fungi, insects and mammalian cells and causes mutations and chromosome aberrations.

By inhalation formaldehyde is carcinogenic to the Fischer 344 rat, producing nasal tumors at dose levels that are within the same order of magnitude as those to which humans are exposed.

Formaldehyde may be carcinogenic to species other than the rat and to tissues other than nasal.

Formaldehyde should be presumed to pose a carcinogenic risk to humans.

No information is presently available whether (a) certain individuals may be at greater risk of cancer from formaldehyde exposure, (b) tumors may be expected to arise at nonrespiratory sites as a result of inhalation of formaldehyde by humans, or (c) the effects of formaldehyde exposure may contribute in an additive or synergistic way to the effects of other carcinogens or tumor promoters.

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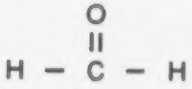
NIOSH

# Current Intelligence Bulletin 34

APRIL 15, 1981

# FORMALDEHYDE:

## EVIDENCE OF CARCINOGENICITY



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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and disseminate new information received by NIOSH that may indicate either the existence of an occupational hazard not previously recognized or a greater hazard than generally known. The Current Intelligence System staff within the Division of Criteria Documentation and Standards Development was responsible for the preparation of this Bulletin.

Current Intelligence Bulletins are disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. The Bulletins are intended to disseminate new data that may affect prevailing perceptions of occupational hazards. They convey important public health information and recommend voluntary protective measures. Current Intelligence Bulletins do not recommend occupational standards, nor are they intended to have any regulatory significance.

## IDENTIFIERS AND SYNONYMS FOR FORMALDEHYDE

Chemical Abstracts Service Registry Number: 50-00-0
NIOSH RTECS Number: LP8925000
Chemical Formula: $CH_2O$

- BFV
- Fannoform
- Formaldehyde, gas
- Formaldehyde, solution
- Formalin
- Formalith
- Formic aldehyde
- Formol
- Fyde
- HCHO
- Ivalon
- Karsan
- Lysoform
- Methanal
- Methyl aldehyde
- Methylene oxide
- Morbicid
- Oxomethane
- Oxymethylene
- Paraform
- Superlysoform

Mention of company name or product does not constitute endorsement by the National Institute for Occupational Safety and Health.

# *FORMALDEHYDE: Evidence of Carcinogenicity*

*April 15, 1981*

*The National Institute for Occupational Safety and Health (NIOSH) recommends that formaldehyde be handled as a potential occupational carcinogen and that appropriate controls be used to reduce worker exposure. These recommendations are based primarily on a Chemical Industry Institute of Toxicology (C I I T) study in which laboratory rats and mice exposed to formaldehyde vapor developed nasal cancer, and are supported by a New York University study where rats exposed to a mixture of formaldehyde and hydrochloric acid vapors developed nasal cancer. Formaldehyde has also been shown to be a mutagen in several short-term laboratory studies. In addition to the carcinogenic potential, other adverse health effects caused by formaldehyde are described. NIOSH requests that producers and distributors of formaldehyde, and of substances and materials containing formaldehyde, give this information to their employees and customers, and that professional and trade associations and unions inform their members.*

## BACKGROUND

Formaldehyde is a colorless, flammable gas with a strong, pungent odor. It can form explosive mixtures with air and oxygen. As an important industrial chemical of major commercial use, formaldehyde is found throughout the environment. In outdoor air it can originate from many sources such as incinerators, photochemical smog, and engine exhaust. Atmospheric levels of formaldehyde have been reported to range from less than 0.005 ppm to 0.06 ppm near industrial outlets or in areas of heavy smog. Workers who smoke are exposed to additional levels of formaldehyde, since cigarette smoke contains as much as 40 ppm of formaldehyde by volume. Thus, an individual who smokes a pack of cigarettes a day would inhale 0.38 mg,[1,2] whereas occupational exposure to formaldehyde at 3 ppm could result in a daily intake of 29.0 mg.

**Production and Uses** - Formaldehyde is usually manufactured by reacting methanol vapor and air over a catalyst (chemical initiator). This results in formaldehyde containing trace amounts of methanol and formic acid. Formaldehyde is sold mainly as an aqueous (water-based) solution called formalin, which is 37% to 50% formaldehyde by weight. It is also used in its solid form as paraformaldehyde and s-trioxane.[1] The U.S. produced about 6.4 billion pounds of aqueous formaldehyde in 1978.[3] Most of this quantity was used domestically. The U.S. consumption of formaldehyde by the year 1983 will likely exceed 7.5 billion pounds. (See appendix for list of major producers of formaldehyde.)

Half of the formaldehyde produced is used to produce synthetic resins such as urea- and phenol-formaldehyde resins. These resins are used primarily as adhesives when making particleboard, fiberboard, and plywood. Urea-formaldehyde concentrates are used in various coating processes, in paper products, and in making foams for thermal insulation. The textile industry uses formaldehyde for producing creaseproof, crushproof, flame resistant, and shrinkproof fabrics. Acetal resins, made from formaldehyde, are used to mold plastic parts for automobiles, home appliances, hardware, and garden and sporting equipment.[4] Formaldehyde is used in some medicines because it modifies and reduces the toxicity of viruses, venoms, and irritating pollens.[5] The use of formaldehyde in embalming fluids is now required by all state laws.[6]

The widespread use of formaldehyde is due to its high reactivity, colorless nature, purity in commercial form, and low cost. In making other chemicals, it can link similar and dissimilar molecules together. In the paper industry, formaldehyde and its derivatives impart wet strength, as well as shrink and grease resistance. Leather and fur can be tanned by formaldehyde. Formaldehyde is used in the photographic industry because it hardens and insolubilizes the gelatin surfaces of film and papers.[5] The table below lists, in alphabetical order, various products made with or containing formaldehyde.[4]

**TABLE - Product Uses of Formaldehyde**

Adhesives
Cosmetics
Deodorants
Detergents
Dyes
Embalming Fluids
Explosives
Fertilizers
Fiberboard, Plywood (indoor-outdoor),
  Particle board
Hardware, Garden
Filters
Food
Friction Materials
Fuels
Fungicides
Insulation, Foam & Some Others
Intermediate Chemicals
Laminates
Leathers, Fur & Hair
Lubricants, Synthetic
Paints
Paper
Pharmaceuticals
Plastics/moldings (Automobile
  Appliances, and Sporting
  Equipment)
Rubber
Surface Coatings
Textiles
Urethane Resins
Watersoftening Chemicals

**Occupational Exposures** - During a 1972-74 survey, NIOSH estimated that 1.6 million workers were exposed to formaldehyde in more than 60 industrial categories. Of these workers, about 57,000 were exposed to formaldehyde 4 hours or more per day. Nearly one-third of the 1.6 million workers (507,200) were engaged in medical and other health services. Another one-third of them (457,200) were in the following industrial categories: chemicals and allied products, printing and publishing, paper and allied products, machinery (except electrical), retail general merchandise, automotive dealers and service stations, eating and drinking places (i.e., busboys, cooks, dishwashers, etc.), and personal services (such as funeral services and crematories, photographic studios, and dry-cleaning plants). Appendix I lists many of the occupational groups exposed to formaldehyde. However, not all workers in each occupational group are exposed to formaldehyde. Therefore it would be prudent for workers in these groups to check their work environment for formaldehyde or products which contain formaldehyde.[7] Appendix II gives ranges of formaldehyde concentrations, by industry, that were found by NIOSH investigators during the past 10 years.

**Exposure Standards** - The U.S. Department of Labor, Occupational Safety and Health Administration (OSHA) standard for formaldehyde requires an 8-hour time-weighted average (TWA) concentration limit of 3 ppm, a ceiling concentration of 5 ppm, and an acceptable maximum peak above the ceiling concentration of 10 ppm for no more than a total of 30 minutes during an 8-hour shift.[8]

In 1976, NIOSH recommended, based upon the irritant effects of formaldehyde, that employee exposure to formaldehyde in the occupational environment be controlled to a concentration no greater than 1.2 milligrams per cubic meter of air (1 ppm) for any 30-minute sampling period.[9] The carcinogenic potential of formaldehyde was not known at that time, and therefore was not considered in developing the recommendations.

## TOXICITY

**Carcinogenicity/Mutagenicity** - Evidence for the carcinogenicity of formaldehyde was first reported in October 8, 1979. Preliminary data from an ongoing inhalation study of rats and mice, sponsored by the Chemical Industry Institute of Toxicology (C I I T), indicated that for exposures of 15 ppm for 6 hours/day, 5 days/week for 16 months formaldehyde is carcinogenic in rats. Some rats had developed cancer by the 12th month. The study, conducted by Battelle Columbus Laboratories, follows a C I I T protocol using Fischer 344 rats and B6C3F1 mice, exposed in groups of 120 animals of each sex, at each of three exposure levels, plus controls, for 6 hours per day, 5 days per week. The study design calls for groups of animals of both species to be exposed concurrently to either 15, 6, or 2 ppm of formaldehyde vapor.[10]

After 16 months of exposure at 15 ppm, three rats developed squamous cell carcinomas originating in the epithelium of the nasal turbinates. A fourth case of nasal squamous cell carcinoma developed in the group exposed to 6 ppm; however, this cancer appeared to have originated from a different site (i.e., from a layer of the skin on the nose rather than the nasal turbinates). In a second progress report (January 16, 1980), the C I I T stated that between the 16th and the 18th month of exposure, a sharp increase in the number of cases of nasal cancer had been observed in rats exposed to 15 ppm formaldehyde. A total of 36 rats developed squamous cell carcinomas of the nasal turbinates after 18 months of exposure. Up to the 18th month sacrifice, no similar tumor had been observed in rats exposed to 2 or 6 ppm or in mice exposed to 2, 6 or 15 ppm formaldehyde.[11,12]

The C I I T presented its latest interim report at the Third C I I T Conference on Toxicology ( November 20 and 21, 1980).[13] It has shown that after 24 months of exposure to 15 ppm formaldehyde, a total of 93 rats have developed squamous cell carcinomas of the nasal turbinates. Two rats have developed respiratory epithelial carcinomas. Furthermore, two rats exposed to 6 ppm and two mice exposed to 15 ppm formaldehyde have also developed squamous cell carcinomas of the nasal turbinates.

Lesions typical of an enzootic viral infection of the salivary gland, sialodacryoadenitis, were found in rats of all exposure groups at the 12th month necropsy. However, mice did not contract the disease. The possibility that the viral infection contributed to the carcinoma response in the C I I T study cannot be discounted, but it is considered unlikely for the following reasons: 1) mice which were not affected by the viral infection developed the nasal cancer; 2) the signs of infection occurred only for a short period of time during the 11th and 12th month of exposure and the first nasal cancers were detected at the 12th month. Therefore, the nasal cancer had probably already formed by the time of the infection.

Squamous cell carcinoma of the nasal turbinates rarely occurs spontaneously. In two recently completed inhalation studies sponsored by C I I T, involving a total of 1,920 Fischer 344 rats, and in two feeding studies involving 1,680 rats, no similar cancer was observed.[10] At the National Cancer Institute, only two cases of nasal squamous cell carcinoma have been observed in 5,884 unexposed Fischer 344 rats.[14]

The interim data from the C I I T in this study indicate that formaldehyde causes nasal cancer in rats. No factors now apparent would significantly alter the interpretation of the existing results.

Epidemiologic studies conducted to date do not permit a definitive evaluation of the carcinogenic risk of formaldehyde to humans.

Because of the concern of the federal regulatory and research agencies about the exposure of humans to formaldehyde, in January 1980, the Interagency Regulatory Liaison Group (IRLG) reviewed the formaldehyde carcinogenicity data in detail. As a result, the Consumer Product Safety Commission (CPSC) in cooperation with the IRLG agencies, convened a panel of scientists from eight federal agencies under the auspices of the National Toxicology Program to review health data related to formaldehyde. This panel has stated, "It is the conclusion of the Panel that it is prudent to regard formaldehyde as posing a carcinogenic risk to humans."[15]

Most chemicals known to cause cancer are also capable of causing a change in the genetic material within a cell (mutation).[16] Therefore, mutagenicity tests support the results of animal tests to determine carcinogenic potential. Formaldehyde has long been known to be mutagenic. Positive findings of the mutagenicity of formaldehyde have been reported in the following laboratory experimental systems: fruit flies (drosophila), grasshoppers, flowering plants, fungi, and bacteria.[17]

A recent report (October 19, 1979) of the New York University (NYU), Institute of Environmental Medicine supports the CIIT evidence of formaldehyde being a carcinogen in experimental animals.[18] One hundred male Sprague-Dawley rats were exposed to a mixture of formaldehyde and hydrogen chloride (HCl) at concentrations of 14.6 ppm and 10.6 ppm, respectively, for a total of 544 days, 6 hours/day over a period of 814 days. The most important finding was that 25 rats developed squamous cell carcinomas of the nasal cavity, and 2 developed benign papillomas (nonmalignant circumscribed tumor of skin cells) of the nasal cavity. The time from first exposure to death from these cancers ranged from 305 to 705 days (mean: 549 days).

Formaldehyde and HCl can combine in the environment to form the chemical bis (chloromethyl) ether (BCME).[19,20] BCME was first reported to cause cancer in rats by subcutaneous administration in 1969.[21] Since then, inhalation studies have shown that BCME causes lung and nasal cancer in rats.[22,23] The most common type of nasal cancer was esthesioneuroepithelioma (tumor of the nerve tissue) and not squamous cell carcinoma.[22,23]

It is not known if the nasal cancer observed in the NYU mixed exposure study was caused by formaldehyde, HCl, BCME, or a combination of these substances. However, formaldehyde seems the most probable etiologic agent for the following reasons. In the NYU study 27 rats developed nasal tumors, 25 of which were squamous cell carcinomas of the nasal cavity. This type of nasal cancer has been seen infrequently in the BCME inhalation studies and has never been observed to occur spontaneously in the more than 2,000 control animals at NYU over a period of many years.[18] This is the same type of tumor as that produced by formaldehyde in the CIIT study at similar levels of exposure. Second, in the NYU study no rat developed lung cancer as was observed in the BCME inhalation studies. For example, of 40 cancers of the respiratory tract reported in one BCME inhalation study,[23] 14 cancers (13 squamous cell, 1 adenocarcinoma) were from the lung and 26 cancers (17 esthesioneuroepithelioma, 1 squamous cell, and 8 others) were from the nasal cavity.

**Other Health Effects** - The first signs or symptoms noticed on exposure to formaldehyde at concentrations ranging from 0.1 to 5 ppm are burning of the eyes, tearing (lacrimation), and general irritation to the upper respiratory passages. Higher exposures (10 to 20 ppm) may produce coughing, tightening in the chest, a sense of pressure in the head, and palpitation of the heart.[2,24,25] Exposures at 50 - 100 ppm and above can cause serious injury such as collection of fluid in the lungs (pulmonary edema), inflammation of the lungs (pneumonitis), or death.[9]

In one report, five nurses working near an artificial kidney (hemodialysis) machine developed wheezing and recurrent episodes of productive cough.[26] The attacks generally occurred in winter and often followed colds. The formaldehyde used to sterilize the machine was found to have caused this respiratory distress.

Dermatitis due to formaldehyde solutions or formaldehyde-containing resins is a well-recognized problem.[27] After a few days of exposure, a worker may develop a sudden inflammatory (eczematous) reaction of the skin of the eyelids, face, neck, scrotum, and flexor surfaces of the arms. An eczematous reaction may also appear on the fingers, back of the hands, wrists, forearms, and parts of the body that are exposed to the rubbing of clothing. This sometimes occurs after years of repeated exposure.

## RECOMMENDATION

Formaldehyde has induced a rare form of nasal cancer in both Fischer 344 rats and in B6C3F1 mice as reported in an ongoing study by the CIIT. In a second study by NYU, formaldehyde appears to have induced the same type of cancer in Sprague-Dawley rats. Although humans and animals may differ in their susceptibility to specific chemical compounds, any substance that produces cancer in experimental animals should be considered a cancer risk to humans. Formaldehyde has also demonstrated mutagenic activity in several test systems. Although a substance cannot as yet be designated a potential occupational carcinogen based solely on results of mutagenicity tests, positive results in mutagenicity tests should be used as supporting evidence for identifying a potential occupational carcinogen.

Based on these results, NIOSH recommends that formaldehyde be handled in the workplace as a potential occupational carcinogen. Safe levels of exposure to carcinogens have not been demonstrated, but the probability of developing cancer should be reduced by decreasing exposure. An estimate of the extent of the cancer risk to workers exposed to various levels of formaldehyde at or below the current 3 ppm standard has not yet been determined. In the interim NIOSH recommends that, as a prudent public health measure, engineering controls and stringent work practices be employed to reduce occupational exposure to the lowest feasible limit. The "Guidelines for Minimizing Employee Exposure to Formaldehyde", Appendix IV, should be adapted to specific work situations.

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Acting Director

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# APPENDIX I

## Occupations Involving Exposure to Formaldehyde

Accountants
Adult Education Teachers
Advertising Agents and Salesmen
Aeronautical and Astronautical Engineers
Agriculture and Biological Technicans
Air Conditioning, Heating, and Refrigeration
Aircraft
Animal Caretakers, Except Farm
Archivists and Curators
Asbestos and Insulation Workers
Assemblers
Automobile Body Repairmen
Automobile Mechanics
Bakers
Bank Tellers
Barbers
Bartenders
Billing Clerk
Biological Scientists
Bookbinders
Bookkeepers
Bookkeeping and Billing Machine Operators
Bootblacks
Bottling and Canning Operatives
Brickmasons and Stonemasons
Bus Drivers
Busboys
Cabinetmakers
Carpenter Apprentices
Carpenters
Carpenters' Helpers
Carpet Installers
Cashiers
Cement and Concrete Finishers
Chambermaids and Maids, Except Private Household
Checkers, Examiners, and Inspectors; Manufacturers
Chemical Technicians
Chemists
Child Care Workers, Except Private Household
Cleaners and Charwomen
Clerical Supervisions, N.E.C.
Clerical Workers - Miscellaneous
Clerical Workers - Not Specified
Clinical Laboratory Technologists and Technicians
Clothing Ironers and Pressers
Compositors and Typesetters
Computer and Peripheral Equipment Operators
Computer Programmers
Computer Specialists, N.E.C.
Construction Laborers, Except Carpenters' Helper
Cooks, Except Private Household
Counter Clerks, Except food
Craftsmen and Kindred Workers, N.E.C.
Cranemen, Derrickmen, and Hoistmen
Credit men
Cutting Operatives, N.E.C.
Decorators and Window Dressers
Dental Assistants
Dental Hygienists
Dental Laboratory Technicians
Dentists
Designers
Dishwashers
Draftsmen
Dressmakers and Seamstresses, Except Factory
Drill Press Operatives
Dry Wall Installers and Lathers
Duplicating Machine Operators
Dyers
Editors and Reporters
Electric Power Linemen and Cablemen
Electrical and Electronic Engineering Technicians
Electrical and Electronic Engineers
Electrician Apprentices
Electricians
Elevator Operators
Embalmers
Engineering and Science Technicians, N.E.C.
Engineers, N.E.C.
Engravers, Exc. Photoengravers
Estimators and Investigators, N.E.C.
Expediters and Production Controllers
File Clerk
Filers, Polishers, Sanders, and Buffers
Food Counter and Fountain Workers
Food Service Workers, N.E.C., Except Private
Foremen, N.E.C.
Fork Lift and Tow Motor Operatives
Freight and Material Handlers
Funeral Directors
Furnacemen, Smeltermen, and Pourers
Furniture and Wood Finishers
Garage Workers and Gas Station Attendants
Gardeners and Groundskeepers, Exc. Farm
Geologists
Glaziers
Graders and Sorters, Manufacturing
Grinding Machine Operatives
Guards and Watchmen
Hairdressers and Cosmetologists
Health Administrators
Health Aides, Except Nursing
Health Record Technologists and Technicians
Health Technologists and Technicians, N.E.C.
Heat Treaters, Annealers, and Temperers
Heavy Equipment Mechanics, Including Diesel
Household Appliance and Accessory Installers
Housekeepers, Except Private Household
Industrial Engineering Technicians
Industrial Engineers
Inspectors, N.E.C.
Insurance Adjusters, Examiners, and Investigators
Insurance Agents, Brokers, and Underwriters
Janitors and Sextons
Jewelers and Watchmakers
Job and Die Setters, Metal
Key Punch Operators
Laborers - Miscellaneous
Laborers - Not Specified
Lathe and Milling Machine Operatives
Laundry and Dry Cleaning Operatives, N.E.C.
Librarians
Loom Fixers
Machine Operatives - Miscellaneous Specified
Machine Operatives - Not Specified
Machinists
Mail Handlers, Except Post Office
Managers and Administrators, N.E.C.
Meat Cutters and Butchers, Except Manufacturing
Meat Cutters and Butchers, Manufacturing
Mechanic, Exc. Auto, Apprentices
Mechanical Engineers
Mechanics and Repairmen - Miscellaneous
Mechanics and Repairmen - Not Specified
Metal Platers
Millwrights
Mine Operatives, N.E.C.
Mixing Operatives
Molders, Metal
Motion Picture Projectionists
Nursing Aides, Orderlies, and Attendants
Office Machine Operators, N.E.C.
Office Managers, N.E.C.
Officers, Pilots, and Pursers; Ship
Oilers and Greasers, Exc. Auto
Operations and Systems Researchers and Analysers
Operatives - Miscellaneous
Operatives - Not Specified
Opticians, and Lens Grinders and Polishers
Packers and Wrappers, Except Meat and Produce
Painters and Sculptors
Painters, Construction and Maintenance
Painters, Manufactured Articles
Pattern and Model Makers, Except Paper
Payroll and Timekeeping Clerks
Personal Service, N.E.C. - Attendants
Personnel and Labor Relations Workers
Pharmacists
Photoengravers and Lithographers
Photographers
Photographic Process Workers
Physicians, Medical and Osteopathic
Plumbers and Pipe Fitters
Podiatrists
Practical Nurses
Precision Machine Operativas, N.E.C.
Pressmen and Plate Printers, Printing
Pressman Apprentices
Punch and Stamping Press Operatives
Purchasing Agents and Buyers, N.E.C.
Radio and Television
Radiologic Technologists and Technicians
Receptionists
Recreation and Amusement - Attendants
Recreation Workers
Registered Nurses
Research Workers, not specified
Restaurant, Cafeteria, and Bar Managers
Riveters and Fasteners
Sailors and Deckhands
Sales Managers and Department Heads, Retail Trade
Sales Managers, Except Retail Trade
Salesmen and Sales Clerks, N.E.C.
Sawyers
Secretaries, N.E.C.
Sheetmetal Workers and Tinsmiths
Shipping and Receiving Clerks
Shoe Repairmen
Shoemaking Machine Operatives
Sign Painters and Letterers
Social Workers
Solderers
Specified Craft Apprentices, N.E.C.
Spinners, Twisters, and Winders
Stationary Engineers
Stationary Firemen
Statistical Clerks
Statisticians
Stenographers
Stock Clerks and Storekeepers
Stock Handlers
Tailors
Teachers, Except College and University, N.E.C.
Technicians, N.E.C.
Telephone Installers and Repairmen
Telephone Linemen and Splicers
Telephone Operators
Textile Operatives, N.E.C.
Therapists
Therapy Assistants
Ticket, Station, and Express Agents
Tile Setters
Tool and Die Maker Apprentices
Tool and Die Makers
Truck Drivers
Typists
Upholsterers
Vehicle Washers and Equipment Cleaners
Veterinarians
Waiters
Warehousemen, N.E.C.
Weighers
Welders and Flame-cutters
Winding Operatives, N.E.C.
Writers, Artists, and Entertainers, N.E.C.

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his list of occupational groups is primarily a list of specific job titles and therefore a generic classification such as textile workers will be made up of several groups (e.g., foremen, machine operative, clothing ironer, etc.).

N.E.C. - Not elsewhere classified

## APPENDIX II

Some Formaldehyde Concentrations, by Industry, from NIOSH Industrial Hygiene Surveys.

| Industry | Formaldehyde Level |
|---|---|
| Fertilizer Production | 0.2 - 1.9 ppm |
| Dyestuffs | <0.1 - 5.9 ppm |
| Textile Manufacture | <0.1 - 1.4 ppm |
| Resins (Non-foundry) | <0.1 - 5.5 ppm |
| Bronze Foundry | 0.12 - 8.0 ppm |
| Iron Foundry | <0.02 - 18.3 ppm |
| Treated Paper | 0.14 - 0.99 ppm |
| Hospital Autopsy Room | 2.2 - 7.9 ppm |
| Plywood Industry | 1.0 - 2.5 ppm |

This information was adapted from a written communication from Richard A. Keenlyside, M.D., Medical Officer, NIOSH to the Deputy Director, NIOSH, November 7, 1980.

## APPENDIX III

List of Major Manufacturers of Formaldehyde

Allied Chemical Corporation
Borden, Inc.
Celanese Corporation
E. I. du Pont de Nemours and Co., Inc.
GAF Corporation
Georgia-Pacific Corporation
Getty Oil, Inc.
Gulf Oil Corporation
Hercules, Inc.
International Minerals and Chemical Corporation
Monsanto Company
Occidental Petroleum Corporation
Reichold Chemicals, Inc.
Tenneco, Inc.
Univar Corporation
Wright Chemical Corporation

# APPENDIX IV

## GUIDELINES FOR MINIMIZING EMPLOYEE EXPOSURE TO FORMALDEHYDE

NIOSH recommends that formaldehyde be handled in the workplace as a potential occupational carcinogen. Exposure should be limited to as few employees as possible, while minimizing workplace exposure levels. The area in which formaldehyde is used should be restricted to only those employees essential to the process or operation. The guidelines listed below are general in nature and should be adapted to specific work situations as required.

### EXPOSURE MONITORING

Initial and routine employee exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of employee exposure and to ensure that controls are effective.

The NIOSH Occupational Exposure Sampling Strategy Manual,[1] may be helpful in developing efficient programs to monitor employee exposure to formaldehyde. The manual discusses determination of the need for exposure measurements and selection of sampling times.

Employee exposure measurements should primarily consist of 8-hour TWA (time-weighted average) exposure estimates calculated from personal or breathing zone samples (air that would most nearly represent that inhaled by the employees). In addition, short term samples should be taken during periods of maximum expected exposure by using all available knowledge of the area, employee work procedures, and processes. Area and source measurements may be useful to identify problem areas, processes, and operations.

### CONTROLLING EMPLOYEE EXPOSURE

There are four basic methods of limiting employee exposure to formaldehyde. None of these is a simple industrial hygiene or management decision and careful planning and thought should be used prior to implementation.

**o Product Substitution**

The substitution of an alternative material with a lower potential health risk is an important method for reducing exposure. However, extreme care must be used when selecting possible substitutes. Alternatives to formaldehyde should be fully evaluated with regard to possible health effects prior to selection.

**o Contaminant Controls**

The most effective control of airborne concentrations of formaldehyde is at the source of contamination by enclosure of the operation and/or use of local exhaust ventilation. Guidelines for selected processes and operations can be found in the NIOSH Recommended Industrial Ventilation Guidelines:[2]

When enclosing a process or operation, a slight vacuum should be used to create negative pressure so that leakage will result in the flow of external air into the enclosure and minimize contamination of the workplace. This can be accomplished with a well-designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the work atmosphere.

Ventilation equipment should be checked at least every three months to ensure adequate performance. System effectiveness should be checked soon after any change in production, process, or control which might result in significant increases in airborne exposure to formaldehyde.

**o Employee Isolation**

If feasible, employees may be isolated from direct contact with the work environment by the use of automated equipment operated by personnel observing from a closed control booth or room. The control room is maintained at a greater air pressure than that surrounding the process equipment so that air flow is out of, rather than into, the room. This type of control will not protect those employees that must do process checks, adjustments, maintenance, and related operations. These employees will need to use personal protective equipment.

**o Personal Protective Equipment**

The use of personal protective equipment, which may include respirators, goggles, gloves, etc., should not be used as the only means to prevent or minimize exposure during routine operations.

However, exposure to formaldehyde can be controlled with the use of this equipment:

- During the time period necessary to install or implement engineering or work practice controls; or

- In work situations in which engineering and work practice controls have proven ineffective; or,

- For maintenance; or
- For operations which require entry into tanks or closed vessels; or
- In emergencies.

Proper maintenance procedures, good housekeeping in the work area, and employee education are all vital aspects of a good control program. Employees should be informed as to the nature of the hazard, its control, and appropriate personal hygiene procedures.

## MEDICAL SURVEILLANCE

Effects such as upper respiratory irritation or dermatitis should alert management that unacceptable exposure to formaldehyde is occurring. A medical surveillance program should be made available that can evaluate these effects. In addition, skin protection should be stressed in the workplace to keep the number of new cases of dermatitis to a minimum.

## AVAILABILITY OF REFERENCES

(1) From GPO as #017-033-00247-9 for $2.75.
(2) From GPO as #017-033-00136-7 for $3.90.

GPO publications can be ordered from:

Superintendent of Documents
U.S. Government Printing Office
Washington, D.C. 20402

## CUMULATIVE LIST OF NIOSH CURRENT INTELLIGENCE BULLETINS

| | | |
|---|---|---|
| 1. | Chloroprene | - January 20, 1975 |
| 2. | Trichloroethylene (TCE) | - June 6, 1975 |
| 3. | Ethylene Dibromide (EDB) | - July 7, 1975 |
| 4. | Chrome Pigment | - June 24, 1975<br>- October 7, 1975<br>- October 8, 1976 |
| 5. | Asbestos - Asbestos Exposure during Servicing of Motor Vehicle Brake and Clutch Assemblies | - August 8, 1975 |
| 6. | Hexamethylphosphoric Triamide (HMPA) | - October 24, 1975 |
| 7. | Polychlorinated Biphenyls (PCBs) | - November 3, 1975<br>- August 20, 1976 |
| 8. | 4,4'-Diaminodiphenylmethane (DDM) | - January 30, 1976 |
| 9. | Chloroform | - March 15, 1976 |
| 10. | Radon Daughters | - May 11, 1976 |
| 11. | Dimethylcarbamoyl Chloride (DMCC) Revised | - July 7, 1976 |
| 12. | Diethylcarbamoyl Chloride (DECC) | - July 7, 1976 |
| 13. | Explosive Azide Hazard | - August 16, 1976 |
| 14. | Inorganic Arsenic - Respiratory Protection | - September 27,1976 |
| 15. | Nitrosamines in Cutting Fluids | - October 6, 1976 |
| 16. | Metabolic Precursors of a Known Human Carcinogen, Beta-Naphthylamine | - December 17,1976 |
| 17. | 2-Nitropropane | - April 25, 1977 |
| 18. | Acrylonitrile | - July 1, 1977 |
| 19. | 2,4-Diaminoanisole in Hair and Fur Dyes | - January 13, 1978 |
| 20. | Tetrachloroethylene (Perchloroethylene) | - January 20, 1978 |
| 21. | Trimellitic Anhydride (TMA) | - February 3, 1978 |
| 22. | Ethylene Thiourea (ETU) | - April 11, 1978 |
| 23. | Ethylene Dibromide and Disulfiram Toxic Interaction | - April 11, 1978 |
| 24. | Direct Black 38, Direct Blue 6, and Direct Brown 95 Benzidine Derived Dyes | - April 17, 1978 |
| 25. | Ethylene Dichloride (1,2-Dichloroethane) | - April 19, 1978 |
| 26. | NIAX® Catalyst ESN | - May 22, 1978 |
| 27. | Chloroethanes - Review of Toxicity | - August 21, 1978 |
| 28. | Vinyl Halides - Carcinogenicity | - September 21,1978 |
| 29. | Glycidyl Ethers | - October 12, 1978 |
| 30. | Epichlorohydrin | - October 12, 1978 |
| 31. | Adverse Health Effects of Smoking and the Occupational Environment | - February 5, 1979 |
| 32. | Arsine (Arsenic Hydride) Poisoning in the Workplace | - August 3, 1979 |
| 33. | Radiofrequency (RF) Sealers and Heaters: Potential Health Hazards and Their Prevention | - December 4, 1979 |
| 34. | Formaldehyde: Evidence of Carcinogenicity | - April 15, 1981 |

NOTE: Bulletins #1 through #18 and #19 through #30 have been reprinted as NIOSH publications, #78-127 and #79-146 respectively, for the convenience of those that desire a complete series of Current Intelligence Bulletins. Distribution of these publications and single copies of Bulletins #31 and later are available from NIOSH Publications Dissemination, Division of Technical Services, 4676 Columbia Parkway, Cincinnati, Ohio 45226.

UNITED STATES GOVERNMENT
# Memorandum

U.S. CONSUMER PRODUCT
SAFETY COMMISSION

DATE: February 19, 1982

TO: Harry Cohen, Program Manager
HSPP, Office of Program Management
THROUGH: Peter W. Preuss, Ph.D., AED, Health Sciences PWP/AGU
THROUGH: Andrew G. Ulsamer, Ph.D., Director, HSHE AGU

K Gupta MCC
FROM: K. Gupta, D.V.M., Ph.D., and M. Cohn, Ph.D., HSHE

SUBJECT: Health Sciences Analysis of Comments on the Proposed Ban of UFFI.

Health Sciences has reviewed and analyzed several documents recently received by the Commission on the proposed ban of UFFI. These included submissions by C.P. Chemical (January 29, 1982), the Formaldehyde Institute and Dr. Sidney Firstman (January 29, February 4, 12 and 16, 1982), the Small Business Administration (February 2, 1982), Professional Consultants in Occupational Health (January 30, February 9, and 16, 1982), the Chemical Industry Institute of Toxicology (Dr. James Gibson, February 15, 1982), Robert L. Sielken, Jr. (February 15, 1982), Rogers, Hoge and Hills (February 8, 1982), and Georgia Pacific (Kip Howlett, February 16, 1982).

Health Sciences preliminary analysis of the comments received in these submissions does not alter our previously stated conclusions on the adverse health effects, including carcinogenicity, associated with the exposure to formaldehyde emitted by UFFI. Most of the comments in these submissions are similar to those received in earlier submissions and have already been responded to by Health Sciences. An analysis of the few new comments received on the formaldehyde risk assessment and the chromotropic acid procedure are presented in the attached report along with a summary review of the CIIT report, the PCOH submission, and the Todhunter memo.

Attachment

## REVIEW OF THE CIIT REPORT

Preliminary evaluation of the final report of the CIIT bioassay study of formaldehyde in rats and mice did not reveal any information that would alter Health Sciences' previous conclusion that formaldehyde is carcinogenic in animals. The report supports the statements made previously by the staff that the two squamous cell carcinomas observed in rats exposed to 6 ppm, the two squamous cell carcinomas in mice exposed to 15 ppm, and the polypoid adenomas at all exposure levels are related to formaldehyde exposure.

a) The report states "although the two carcinomas were not statistically significant (p greater than 0.0167) in the 6 ppm group, they are probably related to formaldehyde exposure and provide valuable dose-response data."

b) The report states that "it is noteworthy to mention that the frequency of squamous cell carcinoma in mice exposed to 15 ppm of formaldehyde was similar to the frequency of carcinoma formation in the rats exposed to 6 ppm." The report indicates that this difference between the two species is due to their differences in physiological response to irritant inhalation.

c) Regarding the polypoid adenomas, the report states that "although the lesions are not statistically significant in any exposure group, their numerical increase makes them suspect as compound enhanced lesions." The report concludes that "formaldehyde inhalation in rats may also be associated with an increase in the frequency of polypoid adenomas".

In addition, there were a number of other significant observations made in the report including:

- epithelial dysplasia and squamous metaplasia of the upper portions of trachea indicating that tissue changes are not confined to the nose;

- two carcinomas originating from non-metaplastic epithelial cells (that is cells normally present in the nasal passage) in rats exposed to 15 ppm. The presence of these cancers further supports the contention that cytotoxic changes such as ulceration may not be a prerequisite for the carcinogenicity of formaldehyde.

Discussion of the February 10, 1982 Memorandum of John A. Todhunter, Ph.D.

Dr. Todhunter discusses basically three major issues in this memorandum that relate to carcinogenicity of formaldehyde:

1) Free formaldehyde in tissues indicates that there is a threshold for formaldehyde carcinogenicity.

2) The hyperplastic and metaplastic changes reported in the CIIT studies are reversible indicating a threshold and an apparent cytotoxic threshold exists.

3) There are no epidemiological studies that show an increase in cancer in spite of long-term extensive exposure.

In addition, Dr. Todhunter mentions several exposure scenarios related to UFFI.

The memorandum presented no new data nor does it contain new interpretations or evaluations of previous data. The memorandum rather aggregates and synthesizes existing scientific information to argue that formaldehyde does not pose a significant threat to human health. Health Sciences is of the opinion that this argument rests on several incorrect bases or assumptions of fact for which supportive data do not exist, or where existing data contradicts the argument presented as follows: ✓

- Free formaldehyde in tissues indicates that there is a threshold for formaldehyde carcinogenicity.

This premise rests on Dr. Todhunter's assumption that 10-40% of total tissue formaldehyde appears to be free. No basis is provided for this statement. Data from CIIT indicate that there is formaldehyde in tissue but, as Dr. Gibson of CIIT pointed out in his December 15, 1981, presentation to the Commission, the CIIT assay for tissue formaldehyde cannot distinguish between free and bound formaldehyde and that most of the formaldehyde detected is probably bound. From what is known of formaldehyde metabolism and chemistry, there is no reason to think that there would be detectable levels of free formaldehyde available to react with cellular constituents. The Federal Panel on formaldehyde reached a similar conclusion.

At present there is no evidence for a threshold for the carcinogenic effects of formaldehyde or for any other direct acting carcinogen (formaldehyde requires no metabolic activation to react with genetic components). This argument also ignores the interaction of formaldehyde with other carcinogens/carcinogenic processes as shown by the literature.

- The hyperplastic and metaplastic changes reported in the CIIT study are reversible indicating a threshold and there is an apparent cytotoxic threshold.

The hyperplastic and metaplastic responses seen in the CIIT bioassay responses were not completely reversed after 6 months post exposure even in the 2 ppm group; there was very little reversal in the 15 ppm group. As to whether a cytotoxic threshold exists, this presumably rests on the Formaldehyde Institute study involving 40 rats, 20 hamsters and 6 monkeys per dose which is really inadequate for such a determination; it is a 6 month exposure study with a rather limited number of animals. It should be noted that there is no reason to assume that the cytotoxic effects of formaldehyde are a prerequisite for its carcinogenic effects; formaldehyde is after all genotoxic and can interact with other carcinogens. The Federal Panel also reached the same conclusions. Also, other chemicals, acrolein for example, cause many of the same irritation and cytotoxic effects as formaldehyde and yet produce no cancers.

- There are no epidemiological studies that show an increase in cancer in spite of long term and extensive exposure.

The epidemiological studies on formaldehyde performed to date are inadequate to determine whether formaldehyde is a human carcinogen or not. The International Agency for Research on Cancer has reached a similar conclusion. These studies all suffer from small populations and undefined exposure (among other faults). As pointed out by Dr. Todhunter, the levels of formaldehyde to which humans are exposed are not well documented in many instances. Other studies indicate that formaldehyde (and other aldehydes) may be carcinogenic to humans, but these are also not conclusive.

Other points were made by Dr. Todhunter in his memo, but they are of less importance that those discussed above, and will not be presented at this time.

# APPENDIX 5

Natural Resources Defense Council, Inc.
122 EAST 42ND STREET
NEW YORK, N.Y. 10168
212 949-0049

*Washington Office*
1725 I STREET, N.W.
SUITE 600
WASHINGTON, D.C. 20006
202 223-8210

*Western Office*
25 KEARNY STREET
SAN FRANCISCO, CALIF. 94108
415 421-6561

May 25, 1982

Honorable Albert Gore, Chairman
House Committee on Science & Technology
Subcommittee on Oversight & Investigations
819 House Annex #1
Washington, D.C. 20515

Dear Rep. Gore:

At the May 20, 1982 Subcommittee hearing on the recent change in EPA's approach to assessing the risk of carcinogens, as illustrated by the case of formaldehyde, I asked your permission to enter the attached document into the hearing record. The document, entitled "Primer on TSCA Section 4(f)," was prepared by the EPA's Office of General Counsel to interpret the meaning and application of §4(f). It is my understanding that as of the date of the hearing, it represents the only opinion on the meaning of §4(f) ever prepared by the EPA's Office of General Counsel.

Yours truly,

Jacqueline M. Warren

Jacqueline M. Warren
Senior Staff Attorney

*New England Office:* 17 ERIE DRIVE · NATICK, MA. 01760 · 617 655-2656
*Public Lands Institute:* 1720 RACE STREET · DENVER, CO. 80206 · 303 377-9740

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Attachment I

OCT 3 0 1980

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF
GENERAL COUNSEL

SUBJECT: Primer on TSCA Section 4(f)

FROM: David E. Menotti, Associate General Counsel
Toxic Substances Division (A-132T) David E Menotti

Steve Atkinson, Attorney
Toxic Substances Division (A-132T) Steve Atkinson 755-0E70

TO: Steven D. Jellinek, Assistant Administrator
for Pesticides and Toxic Substances (TS-788)

## Introduction

Section 4(f) of the Toxic Substances Control Act (TSCA) became effective on January 1, 1979, two years after the effective date of TSCA. This section generally requires the initiation of control actions (or the announcement of a decision not to act) within a short time after receiving information indicating that a chemical may pose certain particularly serious health problems.*/

---

*/ Section 4(f) "Required Actions" provides that

> (f) REQUIRED ACTIONS.--Upon the receipt of--
>
> (1) any test data required to be submitted under this Act, or
>
> (2) any other information available to the Administrator, which indicates to the Administrator that there may be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant risk of serious or widespread harm to human beings from cancer, gene mutations, or birth defects, the Administrator shall, within the 180-day period beginning on the date of the receipt of such data or information, initiate appropriate action under section 5, 6, or 7 to prevent or reduce to

Section 4(f) imposes significant responsibilities on EPA; it is therefore important that Agency efforts to implement the provision proceed on a sound foundation of understanding of the legal obligations which the section imposes. The purpose of this memorandum is to provide that foundation, through a legal analysis utilizing the available source materials which hold the answers to the meaning of the section--its language and its legislative history.

The memorandum utilizes a "Primer" format. In this approach, a series of questions are used to frame the central issues which must be resolved to understand the meaning of the provision. In the format adopted, each question is posed; the question is then answered in summary form; finally, the legal analysis which has produced the answer is presented.

The questions which are posed and answered in the memorandum are as follows:

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*/ [Footnote continued from p. 1]

> a sufficient extent such risk or publish in the Federal Register a finding that such risk is not unreasonable. For good cause shown the Administrator may extend such period for an additional period of not more than 90 days. The Administrator shall publish in the Federal Register notice of any such extention and the reasons therefor. A finding by the Administrator that a risk is not unreasonable shall be considered agency action for purposes of judicial review under chapter 7 of title 5, United States Code. This subsection shall not take effect until two years after the effective date of this Act."

1. What is the function of Section 4(f) in the TSCA scheme?
2. What chemical regulatory problems require priority designation under Section 4(f)?
3. What is a "significant risk of serious harm" and a "significant risk of widespread harm"?
4. What information does the Administrator need to find that a chemical presents or will present a "significant risk of serious or widespread harm" due to cancer, birth defects or gene mutations?
5. How certain must the Administrator be that a chemical poses a significant risk of serious or widespread harm from cancer, birth defects, or gene mutations, before designating the chemical for priority attention under Section 4(f)?
6. For the purposes of calculating the 180 day deadline for action on priority regulatory candidates, what event constitutes the "receipt" of data or other information?
7. If information necessary to make the requisite Section 4(f) findings is received at different times, what is the "date of receipt" from which the deadline for action is to be calculated?
8. Does Section 4(f) require the Agency to review information in the Agency's possession on the effective date of the section, and determine

whether information on a chemical possessed by the Agency at that time satisfies the Section 4(f) test for priority candidate status?

9. Does information already in the possession of the Agency trigger Section 4(f) if it is resubmitted to the Agency by a petitioner? Can information which is duplicative of information already received by the Agency, or information which does not significantly change the Agency's characterization of a chemical problem trigger Section 4(f) responsibilities?

10. Can the Section 4(f) requirement to initiate appropriate action to address a priority risk be satisfied by

    - the initiation of action under other laws administered by EPA?
    - the initiation of action by other Federal regulatory agencies under their statutory authorities?

11. What are the minimum steps necessary for EPA or another Federal agency to "initiate appropriate action" with respect to a chemical which has been designated as a priority under Section 4(f)?

In reading this memorandum, two general caveats should be kept in mind. First, the memorandum is intended to give general guidance on the obligations imposed by Section 4(f).

To some extent, the precision of the analysis was hampered by the absence of concrete sets of facts to set the stage. Where possible, we compensated for this problem by posing hypotheticals to illustrate concepts and to define ranges of situations which we can expect to encounter. However, while this technique is useful, it is not possible to anticipate all the problems which will arise in our administration of Section 4(f).

Second, several elements of the 4(f) standard convey relatively broad discretion to the Administrator. These elements are discussed in detail in the body of the memorandum. While legal analysis can suggest the outer limits of that discretion, how a decision should be made within those limits is a policy--not a legal--matter. Accordingly, the Agency's implementation of Section 4(f) will require the resolution of a number of difficult policy questions. The resolution of these policy questions is, of course, beyond the scope of this memorandum.

## Question #1

What is the function of Section 4(f) in the TSCA scheme?

## Answer

Section 4(f) has two functions: it identifies certain high priority candidates for regulatory action, and establishes a deadline for deciding whether to initiate regulatory action on chemicals which qualify as priority candidates. Section 4(f) is only one of several "action forcing" provisions in TSCA. However, while Section 4(f) compels action on priority candidate chemicals, Section 4(f) does not provide standards for deciding what regulatory action (if any) should be taken, or procedures for taking action. These standards and procedures are found elsewhere.

## Discussion

The two functions of Section 4(f)--the identification of priorities and the imposition of decision deadlines--are obvious on the face of the section.

Section 4(f) is one of several "action forcing" provisions in TSCA. For example, under Section 4(e), EPA is required to respond within twelve months to recommendations by the Interagency Testing Committee that certain chemicals may be appropriate candidates for issuance of testing rules. This response must consist of either an initiation of rulemaking for testing the chemical, or an explanation of why rulemaking to require testing was not initiated.

Under Section 6(a) of TSCA, if EPA finds that activities involving a chemical present unreasonable risks, the Agency is compelled to issue rules to protect against such risk. TSCA also provides mechanisms by which private citizens may bring suit against the Agency to require it to take certain types of actions. Under Section 20, a person may seek to compel EPA to perform any non-discretionary act under TSCA; Section 21 authorizes suit to compel the Agency to initiate certain types of regulatory actions if EPA fails to initiate these actions in response to a petition.

The general Congressional concerns which prompted inclusion of such action-forcing provisions--fear of bureaucratic lethargy and indecisiveness--are clearly expressed in the legislative history*/ but the specific concerns which prompted the inclusion of 4(f) in the statute are less clear. The Senate Report and Conference Report discussions of Section 4(f) consist almost totally of a repetition of the language from the bill itself, with no reference to the specific purpose or motivation underlying inclusion of the provision.**/ No provision analogous to Section 4(f) was included in the House Bill. Section 4(f) was not discussed in the course of the Senate or House debates. Nor was there any strenuous advocacy for such a provision in testimony before Congressional panels, although a single witness urged that the Senate consider "the usefulness of deadlines

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*/ During 1975 hearings, in response to testimony criticizing the citizen suit provision in the bill, Senator Tunney, a key TSCA supporter, noted the difficulty of getting Federal agencies to take action: "We see literally thousands of decisions being sat upon in Federal agencies ... and a good part of my staff's work is to try and get administrators or bureaucrats to make decisions and to cut through red tape." Toxic Substances Control Act: Hearings on S. 776 Before the Subcomm. on the Environment of the Senate Comm. on Commerce, 94th Cong., 1st Sess. 136 (1975). The Senator returned to the same theme in a statement during Senate consideration of the Conference Report in 1976, noting that the bill's provisions for citizen input into the administrative process were an effective way of ensuring that "bureaucratic lethargy does not prevent the appropriate administration of this vital authority." House Comm. on Interstate and Foreign Commerce, 94th Cong., 2d Sess., Legislative History of the Toxic Substances Control Act at 734 (Committee print) (Dec. 1976). This theme was echoed in testimony of representatives of environmental public interest groups. Ms. Warren, spokesperson

[Footnote continued on next page.]

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*/ [Footnote continued from previous page] for the Environmental Defense Fund pointed out to the Senate EPA's "dismal record in the area of regulation of toxic pollutants in water," supporting this by a statement that no such pollutant had been regulated in the 2-1/2 years following passage of the Federal Water Pollution Control Act. Toxic Substances Control Act: Hearings on S. 776 Before the Subcomm. on the Environment of the Senate Comm. on Commerce, 94th Cong., 1st Sess. 144 (1975). The witness concluded that "the broad administrative discretion which pervades the key provisions of this bill greatly undercuts the potential efficacy of these provisions." *Id.* 145. It should be noted that the version of the bill referred to did not contain many of the action forcing provisions which were eventually enacted. In addition, a representative of the NRDC forcefully suggested that Congress structure TSCA around "precise, mandatory, and time-phased requirements." Otherwise, he stated, Congress would be running the risk that EPA "will not act ... [or] that EPA will take some action but far from enough" or that necessary action would be taken only after "prolonged delay and repeated postponements." Toxic Substances Control Act: Hearings on H.R. 7229, 7448, and 7664 Before the Subcomm. on Consumer Protection and Finance of the House Comm. on Interstate and Foreign Commerce, 94th Cong., 1st Sess. 193 (1975) Statement of J. G. Speth.

**/ House Comm. on Interstate and Foreign Commerce, 94th Cong., 2d Sess., Legislative History of the Toxic Substances Control Act at 174, 675 (Committee Print) (Dec. 1976) [hereinafter cited as "Leg. Hist."].

... on the development of §6 regulation based on submitted test data."*/

The dearth of explicit Congressional discussion on the purposes of Section 4(f) is matched by the almost total lack of explanation of the terms used in the section and of possible problems that might be encountered in its implementation. This paucity of legislative history generally hampers legal analysis of Section 4(f).

Finally, it must be kept in mind that while Section 4(f) identifies candidates and sets decision deadlines, it does not contain rules of decision concerning whether to initiate regulatory action, nor specify procedures for taking action. Thus, the Administrator must look elsewhere in TSCA and to other laws**/ for guidance on these issues. For example, before deciding to initiate action under Section 6 of TSCA to prohibit manufacture of a chemical which EPA has determined may present a significant risk of widespread harm due to cancer, the Administrator must take into account the fact that Section 6 authorizes control action only if EPA finds that the risk presented is unreasonable, taking into account such factors as the benefits of the substance to society, and the economic consequences of the rule. Moreover, in taking action under Section 6, the Administrator must follow the procedures set out in that section.

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*/ Toxic Substances Control Act: Hearings on S. 776 Before the Subcomm. on the Environment of the Senate Comm. on Commerce, 94th Cong., 1st Sess. 152 (1975).

**/ For a discussion of the extent to which the Administrator may look to other laws for solutions to Section 4(f) problems, see Question 10 at pgs. 39-44.

## Question #2

What chemical regulatory problems require priority designation under Section 4(f)?

## Answer

Section 4(f) only designates for priority attention chemicals which appear to pose risks to humans of cancer, birth defects and gene mutations which are especially great, *i.e.*, risks of these effects which appear to be *significant and widespread* or *significant and serious*. Chemicals which appear to pose other risks to human beings or risks to the environment are not covered by Section 4(f), regardless of the apparent scope and magnitude of such risks, nor are chemicals which pose risks of cancer, gene mutations, or birth defects which do not satisfy the Section 4(f) test of apparent seriousness.

## Discussion

Section 4(f) identifies for priority attention a relatively small category of chemical regulatory problems which appear to be especially serious. The formula has three elements, each of which contributes importantly to limiting the coverage of the section.

First, the formula excludes altogether chemicals which are candidates for regulatory action because they pose risks to the environment, *i.e.*, to life forms other than man. In consequence, even chemicals which appear to pose especially serious environmental problems are not covered by Section 4(f).

Second, only three kinds of human health effects--cancer, birth defects, and gene mutations--are identified for priority attention. The human health effects which are excluded make up a rather long list, including some effects which are life threatening or otherwise satisfy reasonable standards of seriousness. For example, chemicals which are acutely poisonous, chemicals which are neurotoxins, and all chemicals which affect the hematopoetic system are not covered by Section 4(f).

Finally, by including the requirement that the chemical present a "significant risk" of "serious harm" or a "significant risk" of "widespread harm," the formula limits the coverage of the section to chemicals which pose risks of cancer, gene mutation, or birth defects which appear to be especially important. The meaning of these terms and the extent they can be defined by legal analysis will be addressed infra.*/ For present purposes, it is sufficient to note that the use of this language clearly limits the coverage of the section by excluding some candidate chemicals which pose risks which appear to be neither "significant" and "widespread" or "significant" and "serious."*/

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*/ See Question 3 at pages 13-15.

It is not surprising that Congress chose to exclude some problems from Section 4(f) coverage, in the process of deciding what problems in its judgment warranted special attention. Congress similarly chose, in Section 4(e), to require the Interagency Testing Committee to give priority attention to chemicals known or suspected of causing cancer, birth defects, or mutations, in its designation of recommended candidates for issuance of Section 4 testing rules. But the legislative history contains little by way of discussion and explanation of the Congressional choices reflected in the Section 4(f) formula (or the directions contained in 4(e)).**/

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*/ It is clear that a risk can be "unreasonable" without being "significant" and "serious" or "significant" and "widespread." This is because the reasonableness of a risk is not measured solely by its magnitude, but by other units, viz., by the benefits which derive from the activity producing the risk (Leg. Hist. 422), the cost of control measures, and the magnitude of the risk reduction which can be achieved. Cf. 45 FR 52628 (Aug. 7, 1980) (The cited document proposes substantial revisions in EPA's procedures for issuance of notices of intent to deny or cancel registration of chemicals for pesticide uses. Such actions may be taken when a pesticide is likely to pose "unreasonable adverse effects.") Thus, a relatively small risk, which might not satisfy a "significance" test, might still be unreasonable if it could be eliminated at no cost, or at costs which are reasonable in light of the risk reduction achieved. In this regard, TSCA differs from the Occupational Safety and Health Act, 29 U.S.C. §651 et seq., which a plurality of the Supreme Court has found limits OSHA's authority to impose control measures to risks which are "significant." Industrial Union Dept., AFL-CIO v. American Petroleum Institute, No. 78-911, ____ U.S. ______ (1980), slip opinion at 29.

**/ Senate Report, Leg. Hist. at 173. The House bill did not require that a priority be given to any particular effects in its version of Section 4(e).

## Question 3

What is a "significant risk of serious harm" and a "significant risk of widespread harm"?

## Answer

It is not possible to define either standard with precision by legal analysis, although the language of the statute and the legislative history provide some clues. About all that can usefully be said is that both standards reflect attempts to define situations of grave apparent gravity; that the "significant and serious" standard covers candidates which appear to pose particularly high risks to a few people; and that the "significant and widespread" standard covers candidates which appear to pose somewhat lower risks to large numbers of people. Within these relatively broad statutory boundaries, the application of these standards involves the exercise of discretion informed by policy.

## Discussion

The term "significant risk" is neither defined in the Act nor discussed in the legislative history. Generally, "significance" is a term which is used to refer to the likelihood that a certain harm will in fact occur. However, there is no clear standard as to when a chance of injury is significant and when it is not, although general agreement might be reached as to the extremes on either side. By not defining the degree of chance of harm which is considered significant, Congress left EPA to implement the concept in light of policy considerations. Of course, there will in most cases be considerable uncertainty as to the degree of risk, and it would be appropriate for EPA to factor this uncertainty into determinations of what risks would be "significant."

Congress also failed to define the terms "serious" and "widespread," or to discuss how it intended the terms to be applied in a Section 4(f) context. However, the terms "serious and widespread" are also utilized in Section 7(f) of TSCA as part of the definition of "imminently hazardous chemical substances" against which EPA may seek injunctive relief.*/ With reference to Section 7, the conferees indicated that "widespread injury" was intended to refer to a "risk affecting a substantial number of people."**/ The term "serious" was distinguished from widespread by the fact that to be "serious" a risk need not effect a substantial number of persons.***/

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*/ Section 7(a) authorizes EPA to commence civil actions to obtain appropriate relief to protect against an "imminently hazardous chemical substance." These substances are in turn defined in Section 7(f) as "a chemical substance or mixture which presents an imminent and unreasonable risk of serious or widespread risk to health or the environment."

**/ Leg. Hist. at 691.

***/ Id.

Neither the statute nor the legislative history provide any guidance on how grave a problem must be to be characterized as either "serious" or "widespread." Clearly, the levels of injury ought to be higher than the minimum necessary for regulation under TSCA, or "serious" and "widespread" lose their meaning in the context of TSCA regulation.*/ Since Congress has not given precise meaning to the "serious" or "widespread" standards, application of these standards requires the exercise of administrative discretion informed by Agency policy.

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*/ Section 6(a) authorizes EPA to control an "unreasonable risk of injury to health or the environment;" the section does not require the Agency to find an unreasonable risk of "serious" or "widespread" harm. However, in Section 6(d) Congress recognized the existence of a subcategory of unreasonable risks--those which posed unreasonable risks of serious or widespread injury, and which required especially expeditious regulatory action. While a Section 6(a) rule generally takes effect only after notice and comment, if the Section 6(d)(2) criteria are met, the rule may take effect on the date of proposal. The contrasting use in Section 6 of the terms "unreasonable risk of injury" and "unreasonable risk of serious or widespread injury" clearly indicates that Congress intended a real distinction between the terms.

## Question 4

What information does the Administrator need to find that a chemical presents or will present a "significant risk of serious or widespread harm" due to cancer, birth defects, or gene mutations?

## Answer

In order to make the requisite finding, EPA must possess reliable information that a chemical will cause one of the designated effects. In addition, the Agency must have sufficient knowledge about exposures to the substance to indicate that, taking into account the toxicity of the substance, the exposure presents a significant risk of serious or widespread harm. However, EPA need not possess any knowledge about the benefits provided by the chemical or any adverse effects of potential regulatory actions.

## Discussion

A determination that a chemical may present a significant risk of serious or widespread harm requires the Agency to perform a preliminary risk assessment on the chemical. There are two types of information which EPA needs to perform a risk assessment:

- information on whether a chemical will cause a certain effect ("effects information"), and
- information on human exposure to the chemical ("exposure information").

The fact that there are two essential components to a risk assessment was acknowledged by Administrator Costle, in his decision to ban temporarily most uses of the herbicides 2,4,5-T and Silvex:

> "There are two components to any [chemical] risk: (1) the toxicological properties of a chemical, and (2) exposure to the chemical. The risk assessment is a summation of the conclusions in each of these areas."*/

While information on both exposure and effects is needed for any risk assessment, the reasons why both kinds of information are necessary are graphically illustrated by birth defects risk assessments. Animal testing is a common first step in a birth defects risk assessment. Animal testing for these effects, however, generally involves testing the chemical at increasing doses until a response is observed, or until a reasonably high "cut-off" dose level is achieved without causing birth defects. If a chemical produces birth defects, the response level is then used to characterize the dose response curve for the chemical, and to calculate a "threshold" level. In consequence, chemicals identified through this method as causing birth defects in animals may cause effects only at substantially higher exposure levels that those to which people are exposed. Therefore, these data are useless by themselves to predict risk, and must be linked with information indicating how close actual human exposure levels are to animal effect levels. On the other hand, knowledge of exposure alone obviously cannot indicate the presence of any particular level of risk. It is only by examining information on both hazard and exposure that EPA can make a determination of the risk which a chemical may pose.

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*/ Decision and Emergency Order Suspending Registrations For the Forestry, Rights-of-Way, and Pasture Uses of 2,4,5-T, 44 F.R. 15874, 15883-84 (March 15, 1979).

Under Section 4(f), priority regulatory candidates are identified on the basis of risk considerations alone. Once a chemical problem is so designated, Section 4(f) provides that regulatory action must be initiated unless the risk is "not unreasonable." Under TSCA, a finding on the reasonableness of a risk requires balancing of the estimated risk against the adverse impacts of actions to protect against that risk*/ -- such as the benefits of the use of a particular substance, the availability of substitute products, and the impact of potential regulatory controls on various aspects of the economy.**/ If the risk of a chemical (with respect to cancer, birth defects, or gene mutations) is very high, it is to be designated as a 4(f) priority without any consideration of its apparent reasonableness; if EPA later finds that the high risk is reasonable, it may on that basis decline to initiate action. Conversely, if a risk is small in magnitude, a priority designation under 4(f) is inappropriate even if it is clear that the control action under Section 6. Because "reasonableness" of a risk is not relevant to the 4(f) priority designation, information relating to reasonableness need not be available to EPA when the designation is made.

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*/ Leg. Hist. at 422.

**/ TSCA Section 6(c).

## Question 5

How certain must the Administrator be that a chemical poses a significant risk of serious or widespread harm from cancer, birth defects, or gene mutations before designating the chemical for priority attention under Section 4(f)?

## Answer

Because Section 4(f) is designed to identify regulatory candidates, a chemical regulatory problem may be designated for priority consideration even if there is a somewhat higher degree of uncertainty about the risk than would be acceptable in taking regulatory action to deal with the problem.

## Discussion

Section 4(f) states that EPA must designate a chemical as a priority candidate when information indicates that there "may be a reasonable basis" to find that a high degree of risk exists from cancer, birth defects, or gene mutations. In contrast, the regulatory authorities provided by TSCA under Sections 5, 6, and 7 generally require EPA or a federal court to find that there "is a reasonable basis to conclude" that an unreasonable risk to health or the environment is presented.

It follows from the difference in language that a 4(f) designation requires less certainty as to the existence of a particular level of risk than the major regulatory provisions of TSCA require with respect to a finding of "unreasonable risk." This distinction is consistent with the different purposes served by these provisions. Section 4(f) designates candidates for expedited regulatory decision-making, and itself imposes no regulatory controls. Instead, it triggers a period of intensive study on whether the Agency should initiate action to control the substance; initiation is only the first step in a process which may eventually lead to promulgation of a regulation.

Neither TSCA nor the legislative history provide any guidance on the degree of certainty which is appropriate in identifying Section 4(f) priority candidates. But it is safe to assume that Congress did not intend chemical problems to enter the Section 4(f) queue unless EPA believes them to present a reasonably high probability of especially great risks to human health. For example, expedited decision-making on a Section 4(f) priority will require a substantial investment of resources. Given limited Agency resources, there will be a reduction of the resources devoted to other chemicals and other TSCA functions when a Section 4(f) candidate is identified and analyzed. To assure that resources are not wasted on evaluation of chemicals which eventually are found to result in no risk, or minor risk, it is apparent that Congress did not intend chemical problems to be designated as priorities under Section 4(f) unless there was a reasonably high probability that those chemicals actually presented especially great risks to human health.

## Question 6

For the purposes of calculating the 180 day deadline for action on priority substances, what event constitutes the "receipt" of data or other information?

## Answer

Both the generally accepted meaning of the word "receipt," and the purposes of Section 4(f), support the conclusion that data or information are "received" when they first come into EPA's possession.

## Discussion

Definition of the point in time at which data or information is received is critical to calculation of Section 4(f) deadlines for required action.

Congress did not define the term "receipt" in Section 4(f), or discuss the concept in the legislative history. There are several possible interpretations of the term. First, receipt could signify the point when information first physically arrives anywhere at EPA. Second, receipt could be defined as the point at which the information is received at a particular place in the Agency (e.g., the Office of Pesticides and Toxic Substances ("OPTS")). Third, receipt might be defined as presentation of the information to a person authorized to determine that the Section 4(f) criteria had been met. (This could be the Administrator or another official to whom the authority had been delegated.)

We have concluded that the first alternative--that "receipt" occurs upon arrival at EPA--is the correct interpretation of the term for Section 4(f) purposes. Generally, words in a statutute are to be given their common meaning,*/ especially in the absence of legislative intent to the contrary,**/ or if a special meaning would defeat the object of the law.***/ Here, the normal, unstrained reading of "receipt" of information is "the act or process of coming into possession" of that information.****/ This interpretation of receipt also serves the purposes of Section 4(f) in setting a deadline for action which is triggered by an event not subject to Agency discretion.

There is little support for the second interpretation (i.e., that "receipt" means receipt by a particular EPA office such as OPTS). Section 27(g) of TSCA directed the creation of an Assistant Administrator for Toxic Substances and assigned that officer prime responsibility for "the collection of data" and "the making of recommendations to the Administrator for regulatory and other actions to carry out the purposes of the Act." However, Section 4(f) itself states that a priority determination could be based upon "any other information available to the Administrator," and the decision deadlines for such priority candidates are to be calculated from "the date of receipt of such data or information." Even assuming that OPTS had sole responsibility for evaluating information and recommending whether a 4(f) determination was appropriate, there is nothing in the language of Section 4(f) to indicate that the decision deadline was intended to be calculated from the date when OPTS received the information.

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*/ See, e.g., Texaco, Inc. v. Federal Power Comm'n., 317 F.2d 796 (10th Cir. 1963).

**/ See, e.g., Kramer v. Government of V.I., 453 F.2d 1246 (3d Cir. 1971).

***/ See, e.g., Miner v. Mechanics Bank of Alexandria, 1 Pet. (26 U.S.) 46, 7 L.Ed. 47 (1828).

****/ Websters New Collegiate Dictionary, 1977.

The third interpretation--i.e., that "receipt" means receipt of the information by an official who has delegated authority to make Section 4(f) findings--is directly in conflict with the action forcing theme of Section 4(f). The essence of that theme is that EPA should not only be given the authority to address chemical problems, but also should be compelled through a variety of methods to act expeditiously in order to overcome what some witnesses and legislators characterized as the real possibility of bureaucratic inertia and delay in tackling problems. [See Question 17, above.] If the Agency is compelled to act only after an event which the Agency can itself control, the action forcing intent of Section 4(f) is eviscerated. It is difficult to see why Congress would establish a strict time schedule, at the same time allowing the Agency broad control over the timing of the event which was to trigger the schedule.

The chief argument in favor of either the second or third alternatives--that is, for interpreting Section 4(f) "receipt" to occur at some point after the arrival of information anywhere at EPA--is a practical one. In most cases, there will be a significant delay from the point when information is first received by EPA until the time when the Agency could conceivably recognize that a Section 4(f) determination was justified; for example, delay could result from the time required to bring the information to the attention of the proper personnel (technical, scientific, or otherwise), who could recognize its significance, determine if there were other data available, and decide whether all the data taken together indicated that a priority problem existed. Delay could be especially great if the information is initially received by a division of the Agency which is not directly concerned with the administration of TSCA or if the problems associated with the chemical are new issues for OPTS or the Agency as a whole. Any delay encountered in determining that a Section 4(f) priority candidate existed could severely compromise EPA's ability to meet the section's deadlines for action.

If Congress was aware of these practical problems, it did not discuss them. Indeed, what little evidence there is seems to suggest that the Congress believed that, with adequate planning, the statutory requirements could be met. Congress in fact delayed the implementation of Section 4(f) for two years after the effective date for the balance of TSCA, for the express purpose of allowing the Administrator to "gear up for making these [Section 4(f)] kind of determinations"*/ and Congress arguably expected that this would be adequate time to develop methods for proper processing of newly received information.

In sum, analysis suggests that the language of Section 4(f) and the purposes of the provision are most consistent with the interpretation that "receipt" takes place at the point when an item of information first comes into possession of any part of EPA.

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*/ Leg. Hist. at 173.

## Question 7

If information necessary to make the requisite 4(f) finding is received at different times, what is the "date of receipt" from which the deadline for action is to be calculated?

## Answer

Generally, the Section 4(f) deadlines are triggered on the date of receipt of an item ~~of~~ information which, when considered with other information previously available to EPA, indicates for the first time that the Section 4(f) criteria have been satisfied. This last item of information may relate either to the effects caused by the chemical or to the types and levels of exposure which are occurring.

## Discussion

Section 4(f) states that priority treatment is to be given to a chemical risk if EPA receives information which indicates that there may be a reasonable basis to conclude that the chemical presents a significant risk of serious or widespread harm due to cancer, birth defects, and gene mutations. As discussed earlier,*/ this finding requires the Agency to perform a preliminary risk assessment, for which the Agency needs both "effects" information and "exposure" information.

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*/ See Question 4, p. 16.

In theory, all the information necessary to identify a chemical risk as a 4(f) priority could be received by EPA at a single time. However, effects information and exposure information would not normally be obtained in this way, partly because they are developed by different scientific and technical disciplines, and partly because it is often a finding on one aspect of the risk equation (e.g., that it causes cancer, or that there is high exposure to it) that motivates development of complementary information needed to determine whether a risk exists, and the magnitude of that risk. Therefore, it is necessary to address under what circumstances the receipt of an item of information, which does not by itself permit the Section 4(f) findings to be made, will trigger priority consideration for a chemical.

There is no indication that Congress meant EPA to consider only "new" data in determining whether a Section 4(f) priority risk existed. In addition, no logical purpose would be served by limiting EPA to consideration of the new data. Thus, an item of new information should be considered in the context of any other information on the chemical available to EPA prior to that time, and priority treatment should be triggered upon the receipt of data which, either alone or when combined with other information available to EPA, supports the Section 4(f) findings.

Under this approach, the question of whether receipt of a particular item of information will trigger Section 4(f) designation depends not only upon the nature of that information, but on the nature of previously received information on a chemical. If EPA receives a report indicating that a chemical is a carcinogen, the question of whether the Section 4(f) finding can be made will depend on the nature of the exposure information available. The clearest case would be when EPA already has on file a completed study, based on monitoring, which indicates that numbers of persons are being exposed to the substance at levels likely to result in a significant risk of serious or widespread harm from cancer. In this case, the Section 4(f) requirements would be triggered when the study indicating carcinogenicity was received. At the other end of the spectrum, if EPA has no exposure data on the substance, receipt of a toxicity study could not lead to identifying the chemical as a priority regulatory candidate. Between these two extremes are an infinite variety of cases.

Section 4(f) also may be invoked in situations in which the last item of information received concerns the nature of exposures to a substance. If EPA has determined that a substance is likely to cause cancer but lacks reliable exposure data, it may attempt to determine the extent of exposure to the substance through use of its information gathering authorities under TSCA section 8, studies, consultation with other agencies, etc. In these cases, the "date of receipt" would be the date when EPA received information from these sources which could be combined with data already in EPA's possession to support a finding that the Section 4(f) test had been satisfied.

## Question 8

Does Section 4(f) require the Agency to review information in the Agency's possession on the effective date of the section, and determine whether information on a chemical possessed by the Agency at that time satisfies the Section 4(f) test for priority candidate status?

## Answer

No. Section 4(f) is triggered by the receipt of information, not the possession of information. Consequently, the section operates prospectively, to require the Administrator to review, assess and react promptly to new information received by the Agency after the effective date of the section. Because it does not look backward, Section 4(f) has no bearing on Agency efforts to address "backlog" chemical regulatory problems--*i.e.*, problems characterized by information in the possession of the Agency on the effective date of the section. However, while Section 4(f) is not applicable to "backlog" problems, the Agency can be held to account for inattention to "backlog" problems under other TSCA sections, including Section 21.

## Discussion

Section 4(f) turns on the concept of receipt. It compels the Agency, upon receipt of test data or other information available to the Administrator, to initiate a review which must culminate, within the time limits set by the section, in the initiation of appropriate action or a finding that the risk is not unreasonable. The emphasis on receipt as a starting point for Section 4(f) analysis suggests strongly that the Congress intended a prospective orientation. Consistent with this, January 1, 1979 was established as the starting date for action under the section. Accordingly, Section 4(f) directs Agency attention to problems which are characterized by the fact that relevant information about them is received after that date. It follows logically from the statutory reliance on "receipt" and its reference to a specified effective date that the reach of this provision demanding expedited treatment does not extend to those chemicals whose risk and exposure data were known to the Agency -- i.e., information about them was in the Agency's possession -- before January 1, 1979.

The choice not to require expedited processing of "old" chemicals is entirely consistent with other provisions of the TSCA, which similarly distinguish between, and provide separate regulatory procedures for, "old" and "new" chemical problems. See, e.g., TSCA Section 5. Thus, "new" chemicals must routinely undergo regulatory scrutiny before they are manufactured; while "old" chemicals, including some for which quite substantial risks were known to the Agency long before the passage of TSCA, are placed on an inventory and allowed to continue in manufacture, processing and use until the Agency affirmatively undertakes regulation.

Section 4(f) might easily have been written to provide procedures for the expedited processing of chemicals for which troubling risk and exposure data were known to the Agency before January 1, 1979. The 1979 amendments to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), for example, made specific provision for reregistration of previously registered pesticides in a section of the Act which is largely concerned with establishing procedures for the prospective registration of new pesticides.*/ That Congress failed to make similar provision for "old" chemical risks in Section 4(f) reinforces the view that those chemicals were intended to be processed through other sections of the Act, and were not intended to be subject to Section 4(f).

Indeed, had Congress intended expedited handling for problems which were known to the Administrator before the effective date of the Act, it would, of necessity, have written Section 4(f) quite differently. As it is written, Section 4(f) contains no guidance for the handling of reasonably foreseeable problems which would accompany any attempt to apply its expedited procedures to a potentially large number of previously identified regulatory candidates. Neither the section nor the legislative history even acknowledges such problems, which would include the necessity in a very short time frame of analyzing all information in the possession of the Agency to identify all chemicals subject to Section 4(f), and the need to reach decisions quickly on those chemicals. It seems unlikely that the Agency could act on a large number of backlog chemicals simultaneously, within the 180 day limit set in Section 4(f). But the Act fails to indicate how EPA is otherwise to organize or respond to the queue that would inevitably result from a retrospective reading of the statute. If silence is intended to imply that the Agency has discretion to address the problems, such a grant would appear to be totally inconsistent with the action forcing theme of Section 4(f).

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*/ Federal Insecticide, Fungicide, and Rodenticide Amendments of 1975, Pub. L. 94-140, §4(c), 89 Stat. 752 (amending Pub. L. 92-516 (1972)) (Provision modified by Pub. L. 95-396 (1978)).

As written, however, the provisions of Section 4(f), requiring the Agency to respond quickly to information, implicitly rest on the assumption that the triggering events will occur sequentially, and that the Agency's burden in responding will be similarly phased. Thus, the pace of Agency response will depend on the receipt of data, as studies are completed and research is made available to the Agency through a variety of channels, and not on the need to respond within 180 days of the effective date of the section to an accumulated backlog of chemicals.

Finally, a provision which directs the Agency to respond quickly to new information is entirely consistent with other purposes of TSCA. It insures that information developed under the testing and information requirements of the Act, which indicate the presence of a serious risk, will be given high priority by the Agency. In this regard, it should be emphasized that Section 4(f) is a subsection of that part of the Act which gives EPA the authority to require the testing of chemical substances and mixtures, and that the subsection itself references the receipt of test data required to be submitted under TSCA, as well as the receipt of "any other information available to the Administrator."

Although Section 4(f) is action forcing only with regard to new evidence of risk and is not applicable to "backlog" problems, other sections of TSCA are designed to hold the Agency to account for inattention to known problems. Sections 20 and 21 set out procedures which may be used to hold the Agency to account when a rule is appropriate under other sections of the Act, and in particular, pursuant to Section 21, when it is "necessary to protect health or the environment against an unreasonable risk of injury to health or the environment."

## Question 9

Does information already in the possession of the Agency trigger Section 4(f) if it is resubmitted to the Agency by a petitioner? Can information which is duplicative of information already received by the Agency, or information which does not significantly change the Agency's characterization of a chemical problem, trigger Section 4(f) responsibilities?

## Answer

Information is received for purposes of Section 4(f) when it is first received by the Agency; subsequent submittals of the information by a petitioner have no Section 4(f) significance. Receipt of redundant information, or information which does not significantly change the Agency's characterization of a chemical problem also has no Section 4(f) significance.

## Discussion

The key event for purpose of Section 4(f) is the date on which information is actually received by the Agency. The organizing principle of the section, and the concept that makes it workable, is that the Agency should be compelled to respond quickly to serious new information. If old and new chemical problems are equally candidates for priority treatment, the capacity of the Agency to respond within the short time limits imposed by the section will be diminished and the relative effectiveness of the provision lost. The likelihood that the Agency can respond in the required time period will continue to diminish as the number of chemicals in the Section 4(f) queue increase.

Accordingly, the logic of the section does not allow "old" chemicals to be turned into "new" chemicals by, for example, the simple resubmission of information previously known to the Agency, for that engenders just the kind of bunching, or bulk processing of chemicals, which the section is ill equipped to handle. Backlog chemicals are appropriately handled under other sections of the act, like Section 21, which recognize the Agency's power to set priorities and to distinguish between relative risks.*/

Similar problems are raised when the Agency receives redundant information about chemicals whose risks have been known to the Agency prior to January 1, 1979. If such information were appropriate to trigger 4(f), certain old problems would become priority projects merely because of the fortuitous receipt of some information about them. This is a highly artificial and ultimately unsatisfactory basis for distinguishing between chemicals for Agency attention, and it would undermine the Agency's efforts to establish priorities for handling "old" problems.

More difficult is receipt of information which is additional but not significantly different, particularly if one recognizes a continuum between that information and the kinds of new information which are appropriate to warrant Section 4(f) expedited treatment. The Agency will have to exercise scientific judgment with respect to such information, to determine where on the continuum the information lies. But the overriding principle is the same; the logic of the Section 4(f) contemplates priority attention only for those chemicals for which serious new data is received after January 1, 1979.

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*/ Under Section 21, when responding to a citizen's petition calling for regulation, the Agency can rank problems and is entitled to argue that the problem proposed for Agency action in the petition is better taken up at a later time because it is less urgent than others the Agency faces. This sort of argument is not contemplated by Section 4(f).

### Answer

Although Section 4(f) explicitly refers only to action under Sections 5, 6, and 7 of TSCA, action under other laws in appropriate cases is authorized. This conclusion is based on the express Congressional concern to avoid regulatory overlap between TSCA and other statutes and the fact that taking action under other statutes in no way conflicts with the Section 4(f) goal of prompt action on priority regulatory problems.

### Discussion

#### a. Action by EPA under other statutes administered by EPA.

Section 4(f) states that priority regulatory candidates must be disposed of either by publication in the *Federal Register* of a determination that no unreasonable risk exists, or by initiation of action under Section 5, 6, or 7 to prevent or reduce the risk. While the statute does not expressly authorize the use of other laws, a persuasive case can be made that other laws may, indeed *must*, be used in appropriate circumstances.

The major TSCA authority for regulation of priority candidates designated under Section 4(f) is likely to be Section 6. Section 6(c) prohibits the Administrator from issuing a Section 6(a) rule if a risk could be eliminated or reduced to a sufficient extent*/ by another law administered in whole or part by EPA, unless EPA finds it in the public interest to use TSCA. Accordingly, if a particular Section 4(f) problem could be handled under another EPA statute with equal efficiency and comparable compliance costs, EPA generally could not act under Section 6.

The responsibility to consider the full range of EPA's available regulatory authorities before taking Section 6(a) actions is applied through Section 9(b) to TSCA generally. Section 9(b) initially imposes a requirement to "coordinate" actions under TSCA with those under other EPA-administered laws. In addition, the section indicates that these other laws "shall" be used if the Administrator determines that a risk could be eliminated or reduced to a sufficient extent by action under those laws. As in Section 6(c), this restriction is qualified, so that even if such other laws would suffice, EPA may act under TSCA if the Administrator determines in his discretion that it would be in the public interest to do so.

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*/ Section 6(c) of TSCA states in relevant part that "if the Administrator determines that a risk of injury could be eliminated or reduced to a sufficient extent by actions taken under another Federal law (or laws) administered in whole or in part by the Administrator, the Administrator may not promulgate a rule under subsection (a) to protect against such a risk of injury unless the Administrator finds, in the Administrator's discretion, that it is in the public interest to protect against such risk under this Act." In making the "public interest" finding, the Administrator must consider "(i) all relevant aspects of the risk ..., (ii) a comparison of the estimated costs of complying ..., and (iii) the relative efficiency of actions under this Act and under [other] such laws ...."

Both Sections 6(c) and 9(b) (and Section 9(a), discussed below) reflect a Congressional effort to balance two contradictory themes. On the one hand, recognizing that there were "conspicuous gaps" in the pre-TSCA chemical control authorities,*/ Congress included broad authority in TSCA. Only chemicals subject to the FDCA, FIFRA, and certain nuclear materials, were specifically removed from the TSCA scheme. On the other hand, Congress was aware of widespread criticisms of overlap and duplication among Federal regulatory agencies,**/ resulting in contradictory regulations and wasted resources both in government and in the private sector. The solution imposed in TSCA requires the Administrator to evaluate his other authorities, and to utilize TSCA only after ascertaining it is in the public interest to do so, considering the cost and efficiency of different regulatory approaches. The policy of avoiding inefficiency and duplication on which Sections 6(c) and 9 is founded is applicable to TSCA generally, and there is no apparent reason to exclude Section 4(f) candidates from its reach.

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*/ Leg. Hist. at 414.

**/ The Senate Report addresses TSCA's "Relationship to other Federal Laws" as a key aspect of the statutory scheme. (Leg. Hist. at 164-5.) Furthermore, in response to arguments raised against TSCA, the Senate Report argued that the bill did not extensively overlap with other regulatory provisions, and discussed the terms of Section 9 as an illustration of that fact. (Leg. Hist. at 167.) While the House Report does not discuss the "overlap" issue in general terms, Section 9(b) of the House bill was substantially the same as the Senate version, and the 6(c) mandate to consider other authorities before using Section 6 is drawn from the House bill.

Finally, none of the purposes of Section 4(f) would be thwarted if EPA initiated action under the Clean Air Act, for example, rather than TSCA. Congress wanted to ensure that priority problems were attacked as soon as possible. In those cases in which TSCA action has a significant advantage over other action under other laws, the Administrator could find that it was in the public interest to utilize Section 6 authorities. Otherwise, the goal of Section 4(f) would be equally or better served under another statute. Finally, because Section 4(f) imposes duties on the Administrator, and the Administrator has the same degree of control over the implementation of these other statutes as with TSCA, there is no reason to believe a given problem would receive any less attention if addressed outside of OPTS.

b. Action by other Agencies

Section 4(f) also does not explicitly recognize the possibility of disposing of Section 4(f) priority regulatory candidates through action by other agencies. Nevertheless, specific provisions of TSCA, including Sections 9(a) and 9(d), and Congressional intent, lead to the conclusion that disposition by other Agencies would satisfy the Section 4(f) requirement.

Under Section 9(a), if the Administrator concludes that an unreasonable risk exists (a prerequisite to actions under Section 6 or Section 7), and determines in his discretion that the risk may be reduced to a "sufficient extent" by actions under a law administered by another Federal agency,*/ he must give the agency administering that law an opportunity to protect against the risk before EPA can use Section 6 or Section 7 of TSCA against the risk. Section 9(a) establishes formal procedures for notifying the other agency of the unreasonable risk, allows EPA to set a time limit on the other agency's response, and specifies those actions by the other agency which would preempt EPA from exercising its TSCA authorities with respect to the risk. In addition, Section 9(d) imposes on the Administrator a responsibility to coordinate actions with other agencies to reduce burdensome duplications.*/

There is no reason to believe that action by another Federal agency would be less satisfactory than EPA action in accomplishing the purposes of Section 4(f). Whether formal or informal, referral would occur only if EPA believed the other agency could address the problem sufficiently. It is true that the problem would no longer be under the control of EPA. However, whether or not EPA or another agency are responsible for the carrying out a regulatory action, Section 4(f) requires an official "initiation of action" within the statutory deadlines. Presumably, once the other agency had "initiated" action on the problem (see question 11, below) it would be committed to completion of the action.

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*/ There are significant differences between TSCA coordination requirements for laws administered by other agencies and laws administered by EPA. First, there is no counterpart to the Section 6(c) language which generally prohibits EPA from utilizing Section 6 to regulate risks which could be addressed more efficiently under other EPA authorities. Second, the Sections 9(a) and 9(b) mandates, while similar, are not identical. The legislative history of Section 9(b) indicates an expectation that the Administrator will actively review other EPA authorities to determine their appropriateness for handling the problem, and in fact the Administrator is expected to present the results of his review when he takes action under 6 or 7. Leg. Hist. at 698. Such a review of other laws administered by other agencies is not explicitly discussed in connection with Section 9(a). Id. at 697.

## Question 11

What are the minimum steps necessary for EPA or another Federal agency to "initiate appropriate action" with respect to a chemical which has been designated as a priority regulatory candidate under Section 4(f)?

## Answer

Initiation of action does not require formal action, such as publication of a proposed rule or an ANPR. As the concept is used elsewhere in TSCA, "initiation of action" requires only official action which begins a process culminating in regulatory action in due course. A formal decision (including a schedule for completion of the action) by an official who has been delegated authority to initiate the kind of action commenced would generally be sufficient.

## Discussion

TSCA does not include a definition of the term "initiate appropriate action," and the legislative history of Section 4(f) contains no useful guidance. However, similar terminology is used elsewhere in TSCA, and the meaning of the term can be obtained by analysis of these provisions and their legislative history.

The term "initiate action" is used in TSCA Section 5(g), Section 9(a), and TSCA Section 21(b)(4)(B).*/ In contrast, the other provisions of TSCA which address the commencement of regulatory efforts describe this commencement in terms of a "proceeding" or a "rulemaking proceeding."*/ Only in the legislative history of Section 9(a) is the meaning of any of these concepts explicitly addressed.

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*/ Section 5(g) requires EPA to publish a statement to explain why, in certain situations, it has not "initiated any action" on a chemical for which a Section 5 notice is submitted. Under Section 21(b)(4)(B), a court shall order EPA to "initiate the action requested by the petitioner" if the petitioner demonstrates that certain findings may be made.

Section 9(a) provides a formal mechanism for requesting other agencies to review a chemical problem identified by EPA. If, following this request, the other agency agrees with EPA's assessment and "initiates action" to protect against the risk, EPA is barred from regulating under its own authorities. Guidance contained in the Conference Report indicates that something less than "formal regulatory action" to protect against the risk in the specified time period is sufficient to meet the "initiate action" requirement. That is, it is sufficient if the other agency has "officially initiated an action which will culminate as soon as possible in effective regulatory action ... and sets forth a general time schedule of steps."**/ This language recognizes that initiation of action involves a level of Agency action less formal than an Advance Notice of Proposed Rulemaking ("ANPR") or a proposed rule, so long as it does memoralize more than a "mere open ended possiblity,"*/ i.e., an official decision to act and a general schedule for completion of the action.

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*/ Section 4(e) requires EPA either to "initiate a rulemaking proceeding" on an ITC-designated chemical, or to publish a notice explaining why it has not been initiated Under Section 5(e), 2(D), a Section 5(e) injunction will be dissolved after submission and evaluation of appropriate data, unless EPA has "initiated a proceeding for the issuance of a rule under §6(a)." Under Section 21, a person may petition the Administrator to "initiate a proceeding for the issuance . . . of a rule . . . or an order."

**/ Leg. Hist. at 697-8.

Further, EPA has consistently taken the position that even where the Act requires "initiation" of a "proceeding" or "rulemaking" this can be satisfied short of proposal of a rule. Section 4(e) requires EPA to "initiate a rulemaking proceeding" within a year of receipt of an Interagency Testing Committee recommendation to promulgate a test for a particular chemical or chemicals. EPA has taken the position that Section 4(e) can be satisfied by publication of an ANPR.**/ Section 5(e) of TSCA includes language similar to Section 4(e), i.e. that EPA "has initiated a proceeding for the issuance of a rule under §6(a)" in order for the court to continue an injunction. In its first action under TSCA Section 5(e), EPA also took the position that publication of an ANPR could constitute "initiation" of a proceeding. ***/

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*/ Id.

**/ Affidavit of Steven D. Jellinek, March 4, 1980, National Resources Defense Council v. Costle, 79 Civ. 2411, 2, 6 (S.D. N.Y. filed ______________).

***/ Proposed Order (company identity confidential), Premanufacture Notices #5AEQ-1279-0079 thru 0084 at 52 (U.S.E.P.A. April 23, 1980).

Therefore, it should be appropriate, for example, to "initiate an action" on a Section 4(f) priority candidate with a document signed by the Administrator (or his delegatee) indicating that a particular EPA office will commence development of regulations addressing the problem. Moreover, a schedule for completing action should be included in the decision document.

There is no evidence that Congress intended "initiation of action" to have a different meaning depending on whether EPA or another agency is the responsible organization. As discussed above, action by other agencies accomplishes the same purposes as does action by EPA under either TSCA or other regulatory authority; the official initiation of action in both cases presumably serves the purpose of committing the agency to act and increasing the chances of an expeditious resolution to the problem. There is no statutory basis for stating that Congress intended the requirements of another agency's initiation of action on a 4(f) chemical to be any less, or more, than required under Section 9(a) generally. Of course, the time limits for action under Section 4(f) may generally be incompatible with the formal

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There is no evidence that Congress intended "initiation of action" to have a different meaning depending on whether EPA or another agency is the responsible organization. As discussed above, action by other agencies accomplishes the same purposes as does action by EPA under either TSCA or other regulatory authority; the official initiation of action in both cases presumably serves the purpose of committing the agency to act and increasing the chances of an expeditious resolution to the problem. There is no statutory basis for stating that Congress intended the requirements of another agency's initiation of action on a 4(f) chemical to be any less, or more, than required under Section 9(a) generally. Of course, the time limits for action under Section 4(f) may generally be incompatible with the formal referral mechanism of Section 9(a).*/ This in turn may force EPA to rely on informal referrals to other agencies so as to allow the other agency time to initiate action within the deadlines established by Section 4(f).

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*/ Under Section 9(a), if EPA determines that a problem could be resolved by another agency, it is required to prepare a report describing the problem and requesting the other Agency to consider it. The other agency must be given at least 90 days to respond; if it agrees with EPA's conclusions, it has up to an additional 90 days to initiate action. Generally, this elaborate referral procedure will probably not be compatible with Section 4(f) requirements.

# APPENDIX 6

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

MAY 19 1982

MEMORANDUM

TO: John A. Todhunter, Ph.D.
Assistant Administrator for
Pesticides and Toxic Substances

FROM: Robert M. Perry COPY ORIGINAL SIGNED BY ROBERT M. PERRY
Associate Administrator for Legal
and Enforcement Counsel and General Counsel

Question: For several years now, EPA has examined the possibility that formaldehyde may pose a risk of cancer to humans. However, the risk data is incomplete, and no EPA official has ever recommended any regulatory action based on it. Instead, these officials have recommended a program of studies to better define formaldehyde's carcinogenic effects and the extent of human exposure.

You have asked whether it would be legal, in these circumstances, to designate formaldehyde as a candidate for accelerated regulatory action under section 4(f) of TSCA.

Answer: No. Section 4(f) is designed to force regulatory action, not further studies. It therefore does not come into play until EPA has enough information on risk to responsibly evaluate the need for regulatory action.

## Discussion

### I. Section 4(f) Contemplates Action, Not Studies.

Section 4(f) of the Toxic Substances Control Act provides that whenever the Administrator of EPA receives information

> which indicates to the Administrator that there may be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant risk of serious or widespread harm to human beings from cancer, gene mutations or birth defects, the Administrator shall [within 180 days] initiate appropriate action under section 5, 6, or 7 to prevent or reduce to a sufficient extent such risk or publish in the Federal Register a finding that such risk is not unreasonable.

Sections 5, 6, and 7 are the provisions of TSCA that authorize substantive controls on chemicals. Section 6 allows EPA to impose a wide range of controls on existing chemicals. Section 7 authorizes actions in Federal district court against a chemical that presents an "imminent hazard". Section 5 requires "premanufacture notice" to EPA before putting a new chemical on the market, and allows EPA to prevent the introduction of a new chemical into commerce in appropriate circumstances.

TSCA also contains two sections - section 4 and section 8- that allow EPA to gather information on chemicals, but they are not cross-referenced in section 4(f). By citing the TSCA provisions that authorize regulatory action, and not those that authorize only studies, section 4(f) indicates that only regulatory action satisfies its requirements. The text of the section confirms that interpretation when it calls on EPA by the end of the 180 day section 4(f) period either to initiate action to "prevent or reduce to a sufficient extent" the risk a section 4(f) chemical presents, or else explain why such action is not needed. "Prevent" and "reduce" are words generally used to describe substantive action, not to describe studies.

### II. EPA Must Have Substantial Risk Information Before The Section 4(f) Process Begins.

Though section 4(f) contemplates a decision on regulation after reviewing a designated chemical, it does not change the legal standards that must be met before a chemical may be regulated under TSCA. Generally speaking, EPA may only regulate under TSCA to prevent or reduce an "unreasonable risk", which the law defines as a risk that is unreasonable taking into account all elements of risk and benefit. Indeed, section 4(f) explicitly incorporates this test by instructing the Administrator at the end of 180 days either to decide to regulate a chemical (which requires an "unreasonable risk" finding) or to find that the risk it poses is "not unreasonable" (and therefore no regulation is necessary).

EPA, therefore, must end the section 4(f) process with a balancing of risks and benefits. To begin it, however, EPA need only consider risks. The statute provides for designating under section 4(f) any chemical which the available information indicates "presents a significant risk of serious or widespread harm to human beings from cancer, gene mutations, or birth defects." There is no reference to benefits.

The question here is how much evidence of risk the statute requires to begin a procedure that ends six months later in an informed comparison of risks and benefits sufficient to start the regulatory process. [1]

Section 4(f) would not make any sense if EPA read it as requiring the 180 day clock to start whenever EPA received some evidence of the risks it specifies, even though the information was far short of what was needed to support regulatory action.

The statute contemplates that EPA will begin the section 4(f) process based on risk information. If that information approaches the level needed to support regulatory action, the 180 day deadline serves the action-forcing purpose of compelling EPA to explore the benefits of the chemical, balance them against the risks, and reach a decision on whether to regulate within six months. To go beyond that, and force EPA to start the section 4(f) process when the risk information itself is severely incomplete, would rob section 4(f) of meaning by making it impossible to reach a responsible decision on regulation, under the statutory standards, within the allowed period.

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1/ We do not believe that actual publication of a Notice of Proposed Rulemaking is required to meet this test. We do believe, however, that an internal policy decision to move toward regulation, as opposed to studying the problem further, is required.

# APPENDIX 7

NEW YORK UNIVERSITY MEDICAL CENTER
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January 29, 1982

Mr. Thorne Auchter
Assistant Secretary for Occupational
Safety and Health
OSHA, Room S-2315
3rd and Constitution Avenues, N.W.
Washington, D.C. 20210

Mrs. Anne M. Gorsuch, Administrator
U.S. Environmental Protection Agency
401 M Street, S.W
Washington, D.C. 20460

Ms. Nancy H. Steorts, Chairman
Consumer Product Safety Commission
1111 18th Street, N.W.
Washington, D.C. 20207

Dear Mr. Auchter, Mrs. Gorsuch, and Ms. Steorts:

It has come to our attention that EPA, OSHA, and possibly other federal regulatory agencies, may be planning not to take immediate protective action on formaldehyde, in spite of substantial evidence for its carcinogenicity from animal bioassays. We are concerned about the possibility of such a departure from established public health policy. It would conflict with the prevailing views of the scientific community and would set a precedent which could hamper future regulatory action on other carcinogens.

There is general agreement among experts in chemical carcinogenesis that a substance which causes cancer in significant numbers of experimental animals in well-conducted assays poses a presumptive carcinogenic risk to some humans, even in the absence of confirmatory epidemiological data. While negative human data can define the upper limit of risk to man, there is no recognized method as yet for establishing the existence of a threshold for a carcinogen in the human population. These principles, which are accepted throughout the world, have served for many years as the basis for sound public health policy and regulatory action on carcinogens.

While we recognize the need to weigh carefully all relevant considerations in arriving at a socially acceptable regulatory decision on any substance, especially a chemical as widely used and economically important as formaldehyde, failure to heed clear-cut experimental evidence of carcinogenicity constitutes a grievous mistake in our judgement. We fail to see why the identification of formaldehyde as a presumptive carcinogen, and prudent measures to restrict exposure to the substance, would necessarily cause excessive econonic damage. Many known carcinogens--including ionizing radiation, asbestos, and vinyl chloride, to name only a few--enjoy wide use in spite of the safeguards that limit their risks to human populations.

To compare our views on this subject with those of our colleagues, we have consulted several of the world's leading authorities on chemical carcinogenesis for their opinions. The replies we have received from them thus far are unanimous in supporting the principle that definitive demonstration of carcinogenicity in well-conducted animal bioassays suffices to provide evidence of presumptive carcinogenicity for the human population.

We respectfully submit this letter in the hope that you will find it helpful. If there is anything further we can do to assist you in this matter, please don't hesitate to call on us.

Sincerely,

Arthur C Upton

Arthur C. Upton, M.D.
Professor and Chairman
Department of Environmental Medicine
New York University School of Medicine

I Bernard Weinstein /C

I. Bernard Weinstein
Professor of Medicine & Environmental Sciences
Columbia University College of Physicians and Surgeons

ACU:jg
cc: Dr. Vincent T. DeVita, Jr., Director, NCI
Dr. Michael Gough, Director, Health Program, OTA
Dr. John Hernandez, Jr., Deputy Administrator, EPA
Dr. George A. Keyworth II, President's Science Advisor, Office of Science and Technology
Dr. J. Donald Millar, Director, NIOSH, CDC
Dr. Robert A. Neal, President, CIIT
Dr. Henry C. Pitot, Director, Dept. Oncology, McArdle Lab
Dr. Frank Press, President, NAS
Dr. David P. Rall, Director, NIEHS
Dr. Frank J. Rauscher, Jr., Sr. VP for Research, ACS
Mr. Robert A. Roland, President, Chemical Mfgs. Assoc., Inc.
Mr. Sheldon Samuels, Director, Health, Safety and Env., AFL-CIO

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AUG 2[illegible]
Office of the Assistant [illegible]
For Pesticides and [illegible]

DATE: August 17, 1981

TO:
Dr. Vincent T. DeVita, Director, NCI
Dr. Peter W. Preuss, Associate Executive Director for Health Sciences, U.S. Consumer Product Safety Commission
Dr. J. Donald Millar, Director, NIOSH
Mr. Thorne Auchter, Assistant Secretary, OSHA
Mrs. Anne M. Gorsuch, Administrator, U.S. EPA
Dr. John W. Hernandez, Jr., Deputy Administrator, U.S. EPA
✓ Dr. John A. Todhunter, Assistant Administrator for Pesticides and Toxic Substances, U.S. EPA
Dr. Andrew P. Jovanovich, Acting Assistant Administrator for Research and Development, U.S. EPA
Dr. David P. Rall, Director, NIEHS
Dr. Richard H. Adamson, Acting Director, Division of Cancer Cause and Prevention, NCI
Mr. Sheldon Samuels, Director, Health, Safety and Environment, Industrial Union Department, AFL-CIO
Mr. Robert A. Roland, President, Chemical Manufacturers Association

FROM: Dr. Arthur Upton, Professor and Chairman

Studies under way at our Institute provide decisive confirmation of the Chemical Industry Institute of Toxicology findings that formaldehyde induces squamous cell carcinoma in the nasal cavity of rats. It also confirms the earlier findings reported on October 19, 1979 by Dr. Norton Nelson, my predecessor as chairman of this department, to the effect that combined exposure to formaldehyde and hydrochloric acid gases also induces squamous cell carcinoma of the nasal cavity in rats.

In the experiment reported by Dr. Nelson, a group of 100 male Sprague-Dawley rats was exposed to hydrochloric acid and formaldehyde at mean concentrations of 10.6 and 14.6 ppm for a total of 544 6-hour exposures over a period of 814 days. Among the exposed animals, there were 25 squamous cell carcinomas of the nasal cavity, all of which were highly destructive and grossly visible. There was a zero incidence of nasal cancers in the 100 concurrent controls. Also, we have not observed a single grossly visible spontaneous nasal cancer in 1920 control rats over a period of 14 years.

In our ongoing experiment, we have repeated the combined exposure to HCHO and HCl at average concentrations of 14 ppm and 10 ppm, respectively, as well as separate exposures to HCHO and HCl at the same concentrations used in the combined exposures. As before, male Sprague Dawley rats were used with 100 animals per group, including air sham-exposed controls. After a total of 382 6-hour exposures over a period of 588 days, we have observed 10 histologically confirmed nasal squamous cell carcinomas in the rats exposed to HCHO alone and none in the controls or in the rats exposed to HCl alone. By the Fisher Exact Test, this HCHO response has a $p = 0.001$ in relationship to the concurrent controls and $10^{-13}$ in relation to the historical controls. The combined exposure to HCHO and HCl produced about the same number of histologically confirmed nasal squamous cell carcinomas as HCHO alone (9 tumors per 100 rats). It is noteworthy that the combined exposure to formaldehyde and the potent irritant, hydrochloric acid, shows about the same carcinogenic effect as formaldehyde, itself, and that hydrochloric acid alone in our study has not yet produced cancer.

I am calling your attention to these findings because formaldehyde is presently under consideration for regulatory action. My colleagues, Dr. Norton Nelson and Dr. Roy Albert share with me the conviction that formaldehyde is decisively carcinogenic in animals and with the evidence for its genotoxicity, it is likely that formaldehyde is a human carcinogen. While the relative potency for animals and man is uncertain, we believe it would be a mistake to ignore the evidence for carcinogenicity on the grounds of negative epidemiology which at best can only set upper limits to the carcinogenic potency in man.

If the carcinogenicity of formaldehyde is ignored, it would mean that no agent could be regarded as carcinogenic in the absence of positive evidence in humans. We hope that Federal regulatory agencies will regard formaldehyde as a carcinogen and find ways to continue its important commercial and scientific uses in a sensibly safe fashion.

AU/mb

# APPENDIX 8

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 12 1981

THE ADMINISTRATOR

MEMORANDUM

SUBJECT: Development of Further Information on DEHP and Formaldehyde

FROM: Anne McGill Gorsuch
Administrator (A-100) 6/12/81

TO: Edwin H. Clark, Acting Assistant Administrator for Pesticides and Toxic Substances (TS-788)

At my request, Dr. John Hernandez has reviewed the materials presented to me on DEHP and an advance copy of the materials on formaldehyde. On the basis of his preliminary review, Dr. Hernandez has advised me that this information is insufficient to allow him to make any recommendation on whether or not these two chemicals should be given priority regulatory status.

Accordingly, I have asked Dr. Hernandez to take such steps as are necessary to identify additional information appropriate for making this decision. As part of this process, he intends to seek out expert advice, and meet with interested industry and the OPTS staff. On the basis of these efforts, I expect in the near future to issue a memorandum providing detailed guidance on what information should be developed.

Dr. Hernandez should be given every assistance in his effort.

## SUMMARY OF MEETINGS

Formaldehyde

Scientific/Technical Sessions:

June 19, 1981
July 28, 1981
August 14, 1981

In addition, Dr. Hernandez met with several representatives of the Formaldehyde Institute on May 27, 1981

DEHP

Scientific/Technical Sessions:

August 20, 1981
September 1, 1981
September 29, 1981

## AGENDA
## FORMALDEHYDE MEETING
Friday, June 19, 1981 - 2:00 pm
West Tower - Room 1103

I. Introduction (15 minutes)

- Dr. Hernandez
- Formaldehyde Institute - RAMEY/BYINGTON
- OPTS MERENDA

II. Animal Data (30 minutes)

- OPTS ARCOS
- Formaldehyde Institute
- Discussion

III. Human Epidemiology (15 minutes)

- Formaldehyde Institute
- OPTS BAILAR
- Discussion

IV. Literature Review (15 minutes)

- OPTS MERENDA → OTHERS
- Formaldehyde Institute DEMOPOLOUS
- Discussion

V. Exposure (15 minutes)

- Formaldehyde Institute
- OPTS DAILEY
- Discussion

VI. Position on Principles of Risk Assessment (15 minutes)

- OPTS GRINDSTAFF
- Formaldehyde Institute
- Discussion

VII. Summary (15 minutes)

- Formaldehyde Institute
- OPTS MERENDA
- Dr. Hernandez questions/conclusions on follow-up

## FORMALDEHYDE QUESTIONS

### Animal Data

A. Formaldehyde Institute

1. What defects do you see in the reviews that have taken place of the CIIT study? What further reviews are appropriate? What is the likelihood that these would change the conclusion?

2. In regard to other animal studies which have not shown carcinogenicity, do you believe that these studies were adequate to show negative results, or merely inconclusive? Why?

3. To what extent is FI's argument about the CIIT study based on the issue of the mechanism of carcinogenicity? What would the implications be for humans?

B. OPTS

1. If the final sacrifice of animals indicated a reversal of effects after cessation of formaldehyde exposure, what would be in the implications for humans?

2. Why do you believe that other animal studies should be characterized as inconclusive?

3. Did you consider the question of alternative mechanisms of carcinogenicity? What would the implications for humans be if inflammation was a major causitive factor?

4. Which persons have reviewed the CIIT data, anad what have their conclusions been?

5. What is your evaluation of the significance of the negative hamster findings?

### HUMAN EPIDEMIOLOGY

A. Formaldehyde Institute

1. Do you believe that the four existing studies are adequate in terms of sample size and information on exposure levels?

2. Could there be a significant increase in cancer rates which these or any epidemiological studies were not sensitive enough to detect?

3. When will the results of the NCI - Formaldehyde Institute study be available?

B. OPTS

1. Are existing studies best characterized as negative or inconclusive? Why?

2. Have you reviewed methodology of NCI/FI epidemiology study? Will it be sensitive enough to detect the rates of cancer predicted by OPTS' evaluation?

3. What conditions are necessary for carrying out an adequate study?

LITERATURE REVIEW

A. Formaldehyde Institute

1. Is there any evidence in the literature as to formaldehyde's mutagenic potential? If there are data, what is their significance for a finding that formaldehyde is likely to be carcinogenic?

2. What other studies do you believe should be carried out, and how will they substantially improve the reliability of a finding on the carcinogenic potential of formaldehyde?

B. OPTS

1. Are the types of additional studies suggested by the Formaldehyde Institute likely to significantly improve the reliability of present findings?

EXPOSURE

1. Do you have information on exposure levels in uses of highest concern to OPTS (see PRL-1) and do these data substantially differ from the levels the OPTS was using?

2. If exposure data are unreliable, do you have any plans for obtaining more data?

B. OPTS

1. What are the background concentrations of formaldehyde from natural sources? How do these levels compare to levels of exposure believed to occur at the exposures OPTS has tentatively identified as of most concern?

FORMALDEHYDE Session
Environmental Protection Agency
June 19, 1981

| NAME | ORGANIZATION | PHONE |
|---|---|---|
| Ed Klein | EPA/OTS/CCD | 426-2451 |
| Terry Yosie | EPA/SAB | 755-0263 |
| Steve Atkinson | EPA/OGC | 755-0870 |
| Ruth Bell | EPA | 755-0794 |
| Paul Milbauer | EPA/Administrator's Office | 755-0409 |
| Edwin H. Clark, II | EPA/OPTS | 755-0310 |
| Richard Dailey | EPA/OPTS/AD | 755-4860 |
| Joseph C. Arcos | EPA/OPTS/AD | 755-2110 |
| Joseph Merenda | EPA/OTS/AD | 755-8043 |
| Elizabeth Anderson | EPA | 755-3968 |
| James N. Ramey | Formaldehyde Institute | (212)764-8841 |
| Donald Morgan | Formaldehyde Institute | 828-3097 |
| S. John Byington | Formaldehyde Institute | 331-8700 |
| Ernest M. Dixon, MD. | Formaldehyde Institute | (301)881-6920 |
| Kip Howlett | Formaldehyde Institute | (404)491-6583 |
| William E. Fayerweather | Formaldehyde Institute | (302)774-5780 |
| John Bailar | EPA | 426-2532 |
| win Baumel | EPA/OTS/HERD | 426-2532 |
| ck Griesemer | Oak Ridge National Lab | 624-0213 |
| Dick Hill | EPA | 755-4871 |
| Robert Neal | CIIT | (919)541-2070 |
| James Swenberg | CIIT | (919)541-2070 |
| Harry B. Demopoulos | NYU Medical Center | no number |

Formaldehyde Institute Attendees
June 19, 1981

Joel Binder (Dupont)

S. John Byington (Rogers, Hoge, & Hills)

Dr. Harry Demopolous (New York University)

Dr. Ernie Dixon (Tabershaw Occupational Medicine Associates)

William Foyerweather (Dupont)

Kip Howlett (Georgia Pacific Corporation)

Donald Morgan (Cleary, Gottlieb, Steen, & Hamilton)

James Ramsey (Celanese Corporation)

Dr. Erving Tabershaw (Tabershaw Occupational Medicine Associates)

## JUNE 19 FORMALDEHYDE MEETING

### EPA Participants

Joseph J. Merenda, M.S., Director, Assessment Division, Chemical Engineer

Joseph Arcos, D.Sc., Senior Scientist, Chemical Hazard Identification Branch; Chemical Carcinogenesis Expert

Richard Dailey, M.S., Chemical Review and Evaluation Branch; Environmental Scientist; drafted the Priority Review Level I document on formaldehyde

Irwin P. Baumel, Ph.D., Director, Health and Environmental Review Division; Pharmacologist

John Bailar, M.D., Ph.D., Senior Science Advisor, Epidemiology Branch; Epidemiologist/Biostatistician

Gary Grindstaff, M.P.H., Epidemiology Branch; Statistician

Richard N. Hill, M.D., Ph.D., Senior Science Advisor, Office of the Assistant Administrator for Pesticides and Toxic Substances; Geneticist

Elizabeth Anderson, Ph.D., Director, Office of Health and Environmental Assessment; Organic Chemist

Ruth G. Bell, Esq., Acting Associate General Counsel, Toxic Substances Division

### EPA Observers

Edwin H. Clark II, Ph.D., Acting Assistant Administrator for Pesticides and Toxic Substances

Edward Klein, Esq., Director, Chemical Control Division

### Outside Participants

Richard A. Griesemer, D.V.M., Ph.D., Oak Ridge National Laboratory; Chairman, Formaldehyde Panel, National Toxicology Program; Toxicologist

Robert G. Tardiff, Ph.D., National Research Council, Executive Director, Board on Toxicology and Environmental Health Hazards, Toxicologist

James A. Frazier, M.S., National Research Council, Staff Officer, Committee on Aldehydes, Board on Toxicology and Environmental Health Hazards

Robert A. Neal, Ph.D., Chemical Industry Institute of Toxicology; Toxicologist

James Swenberg, Ph.D., Chemical Industry Institute of Toxicology, Pathologist

## 2nd FORMALDEHYDE SESSION

July 28, 1981

(1)

MEMORANDUM

TO: Paul Milbauer

FROM: S. John Byington

RE: Formaldehyde Meeting Participants

July 27, 1981
to be used for
todays mtg. [illegible]

Assuming we resume the schedule at the point of Exposure Data, then:

I. Exposure Data

Kip Howlett, Georgia Pacific (Chairman, Regulatory Affairs Committee, Formaldehyde Institute)

Bill Groah, Hardwood Plywood Manufacturers Association (Vice Chairman, Technical Committee, Formaldehyde Institute)

II. Risk Assessment

Dr. Robert L. Sielken, Jr., Associate Professor, Institute of Statistics, Texas A & M (Ph.D. in Probability and Statistics, Florida State University)

William Fayerweather, E. I. du Pont de Nemours & Company

Plus

Dr. Joel Bender, E. I. du Pont de Nemours & Company (Chairman, Medical Committee, Formaldehyde Institute)

Dr. Ernest Dickson, Tabershaw Associates

III. Conclusion

Dr. Joel Bender

wrap up.

Mr. James Ramey, Celanese Corporation (Chairman, Formaldehyde Institute)

Also attending:

Jack Murray, Executive Director, Formaldehyde Institute

Don Morgan of Cleary, Gottlieb, Steen & Hamilton (General Counsel, Formaldehyde Institute)

John Byington of Rogers Hoge & Hills (Strategic Counsel, Formaldehoye Institute)

| NAME | AFFILIATION/ADDRESS | PHONE |
|---|---|---|
| John Hernandez | Deputy Administrator, EPA | 755-2711 |
| John Todhunter | Assist. Administrator Designate | 755-0310 |
| Gary Grindstaff | HERD/OTS/617B ET | 755-6841 |
| Rich Dailey | OTS/AD | 755-4860 |
| Bill Groah | Hardwood/Plywood Manf. Assoc. | (703) 435-2900 |
| Joseph Arcos | OTS/AD/CHIB | 755-2110 |
| Joseph Merenda | OTS/AD | 755-8043 |
| James M. Ramey | Form Inst. | (212) 764-8841 |
| S. John Byington | Rogers Hage & Hills | (202) 331-8700 |
| Don Morgan | Cleary, Gottlieb, Steen & Hamilton | (202) 828-3097 |
| Bob Sielken | Inst. of Statistics, Texas A&M | (713) 845-3141 |
| Bill Fayerweather | DuPont | (302) 774-5780 |
| Joel Bender | DuPont | (302) 366-5233 |
| Kip Howlett | Georgia Pacific | (404) 491-6583 |
| Ernest M. Dixon, MD | Tabershaw Assoc. | (301) 881-6920 |
| John Bailar | OTS/EPA | 426-2532 |
| Ruth G. Bell | OGC/EPA | 755-0794 |
| Steve Atkinson | OGC/EPA | 755-0870 |
| Dick Griesmer | Oak Ridge National Lab | FTS 624-0213 |
| Betty Anderson | OHEA/EPA | 755-3968 |
| Ed Klein | OTS | 426-2451 |
| John B. Ritch, Jr. | IAO/OTS | 755-3852 |
| Paul Milbauer | EPA/OA | 755-0409 |
| Edwin H. Clark, II | OPTS | 755-0310 |
| Robert G. Tardiff | NAS/NRC | 389-6914 |
| Jane Keller | OTS | 755-6841 |
| Dick Hill | OPTS | 755-4871 |
| Bill Smock | Formaldehyde Institute | (914) 725-1492 |
| Gerald A. Hapka | DuPont | (302) 774-9466 |
| Mary Martha McNamara | Rogers Hoge & Hills | 331-8700 |
| James Swenberg | CIIT | (919) 541-2070 |
| Dr. Gibson | CIIT | (919) 541-2070 |
| Lisa Barrera | EPA/DA | 755-0418 |

FORMALDEHYDE Session
Environmental Protection Agency
August 14, 1981

| NAME | ORGANIZATION | PHONE |
|---|---|---|
| Betty Anderson | EPA/OHEA | 755-3968 |
| Robert McGaughy | EPA/OHEA/CAG | 755-3968 |
| Edwin H. Clark, II | EPA/OPTS | 755-0310 |
| Chao W. Chen | EPA/OHEA/CAG | 245-3040 |
| Ed Klein | EPA/OTS/CCD | 426-2451 |
| Steve Atkinson | EPA/OGC | 755-0870 |
| Jim Nelson | EPA/OGC | 755-0870 |
| Terry Yosie | EPA/SAB | 755-0263 |
| Marilyn Stone | EPA/OTS | 472-3433 |
| Paul Milbauer | EPA/Administrator's Office | 755-0409 |
| Lisa Barrera | EPA/Deputy's Office | 755-0418 |
| Joseph Arcos | EPA/OPTS/AD | 755-2110 |
| Richard Dailey | EPA/OPTS/AD | 755-4860 |
| Robert L. Sielken, Jr. | Texas A&M University | (713)693-7135 |
| E. John Byington | Rogers, Hoge & Hills | 331-8700 |
| James M. Ramey | Formaldehyde Institute | (212)764-8841 |
| Donald L. Morgan | Cleary, Gottlieb, Steen & Hamilton | 828-3097 |
| Joel Bender | DuPont | no number |
| Julia Phillips | DuPont | (302)774-8284 |
| Gerald A. Hapka | DuPont | (302)774-9466 |
| Ernest M. Dixon, Md. | Tabershaw Associates | (301)881-6920 |
| William E. Fayerweather | DuPont | (302)774-5780 |
| Irwin Baumel | EPA/OTS/HERD | 426-2535 |
| Don R. Clay | EPA/OTS | 755-8033 |
| John A. Todhunter | EPA/OPTS/OAA | 755-0310 |
| John W. Hernandez | EPA/Deputy Administrator | 755-2711 |
| Joseph Merenda | EPA/OTS/AD | 755-8043 |
| David Gaylor | FDA/NCTR | 542-4519 |
| Gary F. Grindstaff | EPA/OPTS/HERD | 755-6341 |
| Kip Howlett | Georgia Pacific | (404)491-6583 |
| Henry Heck | CIIT | (919)541-2070 |
| Mary Martha McNamara | Rogers, Hoge & Hills | 331-8700 |
| Jane E. Keller | EPA/OTS | 755-6841 |
| John F. Murray | Formaldehyde Institute | (914)725-1492 |
| Todd W. Thorslund | EPA/OHEA/CAG | 755-3968 |

## APPENDIX 9

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20205

July 21, 1982

Landow Bldg.
Room 4C03

Peter W. Preuss, Ph.D.
Associate Executive Director for
Health Sciences
U.S. Consumer Product Safety Commission
Washington, D. C. 20207

Dear Peter:

Thank you for your letter of July 2 and the copy of the formaldehyde report by the DuPont epidemiology section. I have reviewed the paper with my associate, Dr. Shelia K. Hoar.

The report deals with a case-control study of cancer mortality in relation to formaldehyde exposure. There were 481 cancer deaths during 1957 through 1979 among male employees at eight formaldehyde manufacturing or using plants. For each case, one male employee who was on the DuPont active personnel rolls during the case's last year of employment was selected, matching the case on age (+/- 3 years), adjusted service date (+/- 3 years), plant and payclass (wage or salary). The data were analyzed by tumor site, latent period, duration of exposure, exposure level and frequency, cumulative exposure index, age and year of first exposure, and age and year of death. In none of these analyses was the formaldehyde workers' relative risk of cancer significantly greater than 1.0. The DuPont scientists interpreted excesses in risk for prostatic and bladder cancer to be due to chance.

### STRENGTHS

- DuPont is to be commended for going to great lengths to reconstruct a reasonable estimate for each subject's exposure to formaldehyde. Many sources of information and expertise were used to determine exposure type, level, cumulative dose, duration, and calendar time. The data sources included the work histories, process descriptions, job code dictionaries, air monitoring data, and recollections of long-term employees.
- Some of the exposure assessment procedures were done without reference to any particular study subject (e.g., job code dictionaries) thereby reducing the possibility of observation bias.
- Smoking histories were ascertained by interviewing the living co-workers of deceased subjects, by interviewing the living controls, and by examining existing medical records. The validity of the smoking histories thus obtained is supported by the dose-response relationship seen for lung cancer and cigarette smoking.
- A comprehensive analysis using acceptable statistical methods was done. The thorough analyses included consideration of tumor site, latency, duration, exposure level and frequency, cumulative exposure index, age and year of death, age and year of first exposure, cigarette smoking, payroll class, and company plant.

* The controls were selected from the cases' co-workers thereby minimizing differences in geography, socioeconomic status, time, and "healthy worker" status.

* The investigators showed that the exclusion of persons who left the formaldehyde plants before becoming eligible for a pension probably did not bias the study results. The cancer risk in these "dropouts" would have to be at least five to ten times greater than the risk in the study subjects to change the study's results.

* Every plant first used formaldehyde at least 15 years ago, providing an adequate latent period for the development of cancer.

WEAKNESSES

* A major criticism of the study is the possibility of observation bias. Some living controls were matched to deceased cases. Vital status affects the availability and the quality of data about the study subjects. Personnel departments often destroy or otherwise remove the records of deceased workers. The cases would have fewer workers for whom work histories were available or of good quality compared to the controls which included living active employees. The paper needs to mention the number of controls by vital status and for whom work histories are missing. Also, long-term co-workers are more likely to overestimate a dead man's exposure to a hazardous substance than someone's exposure who was healthy.

  Bias may have been introduced by the differences in vital status between the cases and controls when the investigators were determining smoking histories. Co-workers are likely to overestimate the smoking history of a man who died from cancer while a living employee is likely to underestimate his own smoking history due to either a real change in recent years or a desire to minimize an undesirable habit.

  The study is not based solely on prerecorded exposure information. Therefore, to reduce observation bias, deceased controls should have been matched to deceased cases.

* The cases and controls may have been overmatched on correlates of exposure. Controls matched on plant, payroll class, age, adjusted service date (date hired adjusted for breaks in employment), and length of employment would probably have had similar job histories as the cases. Unless the formaldehyde operations were a small part of a plant's operations, the cases and controls would have almost identical exposure histories by design. This study may thus not be able to detect possible hazardous effects of formaldehyde.

* The DuPont investigators attributed to chance the "slight but statistically nonsignificant elevations in relative risks" for prostatic and bladder cancer. The results deserve further discussion. Although not statistically signficant, the risks were increased as much as 3- to 5-fold for some subgroups and followed the patterns expected if the relationships were causal. For example, the relative risks for both tumors increased with increasing years of exposure to formaldehyde and the cumulative exposure index. Also, the increase in prostatic cancer is consistent with

the study by Wong. Both bladder and prostate cancer are diseases of elderly men. More cases may occur among the DuPont workers as time elapses. Except for the possible unrepresentative selection of controls for the prostate cancer cases, the authors' other explanations for the prostate and bladder cancer findings are not convincing.

* The study lacks adequate statistical power to detect moderate increases in cancer risk for any site other than lung.

* DuPont has cancer incidence data available through its cancer registry which was not used in this mortality study. Although the registry is restricted to active employees while the mortality file also covers retirees, the registry may have had more incident cancer cases than the mortality file had cancer deaths. Why weren't incident data presented or mentioned?

* For various cancer sites, the wage/salary payclass ratio varied from the overall 3:1 ratio (Table IV) which could indicate a relationship to occupational exposures. Interesting sites and ratios included buccal cavity and pharynx (6:1), stomach (4.8:1), liver (9:1), larynx (7:1), kidney (12:1), brain (11:1), malignant melanoma (7:0), and bone (6:1). The ratios were not discussed nor apparently investigated further.

* Table XX fails to adequately address the question of interaction between formaldehyde exposure and smoking. Data from Table VII suggest Table XX still has residual confounding by cigarette smoking. The relative risk for formaldehyde exposure among nonsmokers is needed in addition to Table XX to determine if interaction is occurring.

* Cancer deaths were not included among employees terminated or transferred to a plant not in the study. As indicated by the authors, the reasons for transfer may be related to past chemical exposures.

In summary, DuPont expended great efforts to obtain exposure estimates and smoking histories but may have overmatched on exposure and introduced observation bias by using live controls for dead cases with different data collection techniques for each group. Although the results are of interest, they should be considered preliminary rather than definitive in nature. As you know, our group at NCI is pursuing cohort studies of formaldehyde workers, which I feel should provide useful information in assessing the possible carcinogenic risks of this chemical.

I hope this information is helpful to you. If there are any questions, please feel free to call Dr. Hoar or myself.

Sincerely,

Joseph F. Fraumeni, Jr., M.D.
Associate Director for Field
Studies and Statistics
Division of Cancer Cause and Prevention

August 3, 1982

Bruce Karrh, M.D.
Corporate Medical Director
Employee Relations Department
Medical Division
E. I. Du Pont De Nemours & Company
Wilmington, Delaware 19898

Dear Dr. Karrh:

Thank you for providing NIOSH with a copy of your mortality study entitled, "Epidemiologic Study of Cancer Deaths in Du Pont Workers with Potential Exposure to Formaldehyde".

My staff has reviewed the report and, in general, we were concerned about the analytic methods and study design that were used. Especially important, we found the study to be weak in its statistical power to detect upper respiratory tract tumors. Hence we are concerned about your statement that this study supports the conclusion that airborne formaldehyde levels of 1 ppm time-weighted average and a 2 ppm ceiling provide adequate employee protection.

Because of their interest in the formadehyde issue, I will send a copy of our critique to OSHA and CPSC. We will hold these copies for 15 working days in case you would like to respond to our comments.

Thank you again for providing us with the opportunity to review this most important piece of epidemiologic research.

Sincerely yours,

Philip J. Bierbaum
Acting Director
Division of Surveillance, Hazard
Evaluations and Field Studies

Enclosure

cc:
Dr. Peter Infante, OSHA
Dr. Peter Preuss, CPSC
bcc:
Mr. Philip Bierbaum ✓
Dr. Richard Lemen
Ms. Brenda Coker
M. Hoffmann ATL 0017

# REVIEW OF THE DU PONT STUDY OF CANCER DEATHS IN WORKERS WITH POTENTIAL EXPOSURE TO FORMALDEHYDE

Du Pont is reporting a case control study of 481 cancer deaths and controls at numerous facilities. The risk factor of interest is formaldehyde exposure. The basic concept of this study is an appropriate and imaginative approach. The case control approach is particularly appropriate for addressing this issue since nasal sinus cancers are extremely rare tumors. It is our opinion that there are several problems, however, that need to be mentioned. It appears that improper analytic methods have been used, and the study has weak statistical power. Also, we would question the study design and Du Pont's interpretation of the findings.

## I. Analytic Methods

a) In this study, cases were matched to controls using rather rigid criteria. Each cancer case was matched to a control for age, plant location, sex, payclass and adjusted service date (which is not defined). A matched study design requires analysis which takes into account the matching factors. Unfortunately, a crude analysis was presented in all of the tables related to formaldehyde exposure except for Table VIII. The crude analysis may well bias the results away from showing an association with formaldehyde.

On page 9, the report suggests that adjusted odds ratios were computed for all analyses; however, for descriptive purposes, only crude analyses were presented and that the differences between the crude and adjusted odds ratios were small. Despite the reported small differences between the crude and adjusted ratios, we believe the authors should present the readers with an odds ratio that has been adjusted for the matching factors or at least a distribution of concordant and discordant case-control pairs.

b) This study used a latency assumption in all of its exposure analyses. In general, such an assumption is logical since most cancers are known to require a relatively long period of time to develop from the initial exposure to a carcinogenic agent. However, we do not believe this study used this assumption appropriately. Latency periods for the cancer sites were chosen based on the logistic analysis presented in Table VIII. The authors attempted to choose a period that maximized the exposure odds ratio. The study classified as nonexposed the cases and controls that did not meet the minimum latency requirement. An extreme example of the effect this might have is if an exposed case dies of cancer after having 19 years of latency, a 20 year latency requirement would have classified this case as nonexposed. If the latency for this cancer was really only 15 years, this approach could lead to a serious misclassification bias in the direction of observing no effect. The conventional and appropriate approach to this type of analysis is to exclude exposed cases and controls that do not satisfy the latency requirement rather than including them in the nonexposed category (e.g. Hoover and Cole, N Engl J Med 288:1040-1043,1973). In addition, we believe the data should be analyzed with and without the latency assumption, since this assumption may be incorrect.

## II. Sensitivity - Statistical Power

Based on the estimates presented in Table XXIII, this study was extremely limited in its ability to detect an elevated odds ratio for all respiratory sites except lung, bronchus and trachea. At an 80% power level, this study could only detect an odds ratio of 22.5 for larynx, and 30.7 for buccal cavity and pharynx. Based on U.S. Vital Statistics for males in 1970, approximately one case of nasal-sinus cancer could have been expected, and therefore the power for this site is far lower than for any of the other respiratory sites. These estimates were based on the assumption that 20% of the controls were exposed to formaldehyde. However, only 5% (25/481) of the controls had continuous exposures of greater than 0.1 ppm. The Table presented below presents power and least significant odds ratio estimates for respiratory sites under a 5% exposure assumption. Under this assumption this study has inadequate power for even trachea, bronchus and lung cancer (37% for detecting an odds ratio of 2.0). At an 80% power level, the study could only detect an odds ratio of 2.9 for lung, bronchus and trachea, 57.5 for buccal cavity and pharynx, and 42.5 for larynx.

RESPIRATORY CANCER POWER & LEAST SIGNIFICANT ODDS RATIO (OR)
ESTIMATES FOR DUPONT STUDY[a,b]

| | Lung, Bronchus & Trachea | Buccal Cavity & Pharynx | Larynx |
|---|---|---|---|
| Number of Cases | 181 | 7 | 8 |
| Power to Detect Odds Ratio = 2.0[c] | 37% | 4% | 4% |
| Least Significant Odds Ratio Detectable[d] | 2.9 | 57.5 | 42.5% |

---

a. Estimates derived using the Hewlett Packard programs in Rothman KJ, and Boice JD. Epidemiologic analysis with a Programmable calculator. NIH Publication No. 79-1649, June, 1979.

b. A 5% exposure rate was assumed since this percentage of the controls are exposed continuously to formaldehyde at levels greater than .1 parts per million.

c. Assumes alpha = .05 (1 tail)

d. Assumes alpha = .05 (1 tail) and Power (1-beta) = .80

III. Interpretation of the Findings

a) On page 20, the report states, "These results support the position that airborne formaldehyde levels of 1 ppm TWA and 2 ppm ceiling provide adequate worker protection." Even ignoring the methodologic issues mentioned earlier, we do not believe the results of this study support such a strong statement. First of all, as previously discussed, at best, this study could only detect an odds ratio of 30 for buccal cavity and pharynx, 23 for larynx and had virtually no chance of detecting nasal cancer. Thus, we do not believe a study as statistically weak as this should be used to support the position that an exposure of 1 ppm TWA with a 2 ppm ceiling is safe.

b) In the last paragraph on page 18, the paper states, "We believe that the slight elevations in the prostatic and bladder cancer odds ratios are chance occurrences and are unrelated to the workers' exposure to formaldehyde." We disagree; it is possible that these elevations are not a result of formaldehyde exposure, but it seems less likely that these findings are due to chance. All of the exposure analyses presented suggested a dose response trend for these sites. These findings, particularly for prostatic cancer, are consistent with other studies in the chemical industry. Marsh's study showed a significant (p less than .05) excess (PMR = 196) of prostatic cancer, and a suggestive excess of bladder cancer (2 observed, 0 expected). Wong's study also revealed a statistically significant (p less than .05) excess (SMR = 431) of prostatic cancer in workers with greater than 20 years of latency.

IV. Study Design

a) A major problem with this study's design is that in addition to formaldehyde, exposure to other carcinogens may have occurred. The list of carcinogens in Appendix C include many potential respiratory carcinogens such as asbestos, chromates, and acrylonitrile. As the authors suggest on Page 17, if workers not exposed to formaldehyde were exposed to other carcinogens, this could mask the effects of formaldehyde. However, this study failed to try to account for the influence of these exposures on the study outcome. Perhaps a distribution of cases and controls exposed to these other agents could have been presented.

b) This paper should indicate the eligibility criteria for receiving death benefits from the company's life insurance plan. Deaths covering this plan constituted the pool from which cancer cases in this study were selected. It is possible that these eligibility requirements may have eliminated greater than the estimated (Page 16) 15-20% of the underlying workforce. This might have resulted in a serious negative bias if workers that were more sensitive to the effects of formaldehyde, left the industry prior to meeting the eligibility requirements.

## V. Other Issues

a) Should not the possible confounding influence of race have been studied. For example, prostatic cancer rates differ sharply between blacks and whites.

b) Table XII has an apparent error. 491 controls are listed in the All Sites category. However, there are only supposed to be 481 controls in the study.

c) The report would havc been more complete and easier to evaluate if the numbers of concordant and discordant case control pairs were included in each table. The distribution of cases and controls in terms of latency and exposure duration could have been presented for ease of review.

## VI. Summary

We believe the study is limited by the analytic methods used, the study design, and the low statistical power particularly for upper respiratory cancers (e.g., nasal). In view of these concerns, we do not believe the findings should be interpreted as the authors have suggested that airborne levels of 1 ppm TWA and a 2 ppm ceiling provide adequate worker protection.

Division of Surveillance, Hazard
Evaluations and Field Studies
National Institute for Occupational
Safety and health
August 3, 1982

DU PONT

E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
WILMINGTON, DELAWARE 19898

EMPLOYEE RELATIONS DEPARTMENT
MEDICAL DIVISION

August 24, 1982

Mr. P. J. Bierbaum
Acting Director
Division of Surveillance, Hazard
Evaluations and Field Studies
National Inst. for Occupational Safety & Health
Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati, Ohio 45226

AUG 1982
RECEIVED

Dear Mr. Bierbaum:

I wish to thank you for agreeing, in our August 17 telephone conversation, to provide Du Pont additional time to respond to the NIOSH critique of Du Pont's "Epidemiologic Study of Cancer Deaths in Du Pont Workers With Potential Exposure to Formaldehyde" prior to your forwarding the critique to OSHA and CPSC. I also appreciate your agreement to include a copy of Du Pont's comments when you send the critique to the other Federal agencies.

A copy of our comments is attached. It addresses the concerns which were raised in your August 3 letter and the attached critique.

Please let me know if you have additional comments or questions.

Sincerely,

Bruce W. Karrh, M.D.
Corporate Medical Director

BWK:ceb
Attachment

There's a world of things we're doing something about

## COMMENTS ON THE NOISH DOCUMENT "REVIEW OF THE DU PONT STUDY OF CANCER DEATHS IN WORKERS WITH POTENTIAL EXPOSURE TO FORMALDEHYDE"

This NIOSH critique of the Du Pont study has been reviewed by the study's author and other members of Du Pont's Epidemiology staff. A few general comments will be made and then each specific NIOSH comment will be addressed.

The introductory paragraph of NIOSH's critique is both complimentary and confusing. It states "The basic concept of this study is an appropriate and imaginative approach. The case-control approach is particularly appropriate for addressing this issue since nasal cancers are extremely rare tumors." These statements are complimentary and are very much appreciated. NIOSH, however, in the same paragraph states ". . . we would question the study design and . . .." This statement is confusing in light of the sentences previously quoted.

Specific responses to NIOSH's comments follow:

I. Analytic Methods

a) NIOSH comment:

> ". . . A matched study design requires analysis which takes into account the matching factors. Unfortunately, a crude analysis was presented in all of the tables related to formaldehyde exposure except for Table VIII. The crude analysis may well bias the results away from showing an association with formaldehyde. . . . we believe the authors should present the readers with an odds ratio that has been adjusted for the matching factors or at least a distribution of concordant and discordant case-control pairs."

Du Pont response:

As was stated in our report (p.9), adjusted odds ratios, lower and upper 95% confidence limits on these odds ratios, and two-tailed p-values were computed for all analyses. However, for descriptive purposes and ease of understanding, in most instances only crude (nonadjusted) odds ratios were presented.

Since the differences between crude and adjusted odds ratios were small, presentation of the crude odds ratios should not have caused readers to misinterpret the results. Furthermore, all tests of statistical significance were based on the adjusted analyses.

This approach is the same approach taken by NIOSH in its final report of the Case-Control Study of Eye and Kidney Cancer at the E. I. du Pont de Nemours & Company, Belle, West Virginia Plant (1982). In this NIOSH matched case-control study, the authors state (p.4) "the unmatched results are reported below, since the matched analyses differed little from the unmatched." However, for the Du Pont formaldehyde study, we can supply NIOSH with distributions of concordant and discordant case-control pairs if necessary for understanding our conclusions.

b) NIOSH comment:

". . . The authors attempted to choose a (latent) period that maximized the exposure odds ratio. The study classified as nonexposed the cases and controls that did not meet the minimum latency requirement . . . The conventional and appropriate approach to this type of analysis is to exclude exposed cases and controls that do not satisfy the latency requirement rather than including them in the nonexposed category . . . In addition, we believe the data should be analyzed with and without the latency assumption, since this assumption may be incorrect."

Du Pont response:

We disagree with your position on latency. Latency was treated as it was in order to not dilute any real effects by including irrelevant experience that is unrelated etiologically to the exposure.

According to K. J. Rothman's recent article (1981) on induction and latent periods, ". . . in case-control studies, dilution of effect occurs by considering as relevant exposure a history of exposure outside the time span which corresponds to the range of the empirical induction period . . . ." And "In a case-control study a lifetime exposure history will inevitably underestimate an effect which pertains to exposure at a specific time before disease. Case-control studies employing lifetime exposure histories should be expected to give results which differ, possibly greatly, from those obtained from studies with exposure defined during narrow time windows." And further, "Again, the analysis yielding the largest estimate of effect selects the most-appropriate assumption about the empirical induction period, and gives the best estimate of the undiluted effect . . . . (Emphasis added.)

Cases and person-time experience occurring outside the time window might reasonably be ignored, or included as part of the nonexposed rate." (1) We chose to include cases and controls falling outside of the time window in the nonexposed group.

## II. Sensitivity - Statistical Power

a) NIOSH comment: (summarized)

At best, this study could only detect an odds ratio of 30 for buccal cavity and pharynx, 23 for larynx and had virtually no chance of detecting nasal cancer.

Du Pont response:

We mentioned in our report (p.16, Table XXIII) that the study had limited sensitivity for cancer sites for which there were only a few cases. Even so, the observation that there were no formaldehyde-exposed nasal cancers in this study or in other studies permits us to establish an upper limit on the possible risk of nasal cancer from formaldehyde exposure.

The CIIT study suggested that if formaldehyde were a human carcinogen, then the upper respiratory tract, particularly the nasal cavities, were the most likely targets in humans. Some critics have argued that the lower respiratory tract should also be considered a likely target, since rats are obligate nose breathers but man is not.

The Du Pont study and three other epidemiology studies (Wong, Walrath, and Marsh) of workers exposed to formaldehyde have found no excess risks for cancers of the nasal cavities, respiratory tract, or buccal cavity that could be attributed to formaldehyde exposure.

Although the power of any one study may be limited, the combined negative result with respect to upper and lower respiratory tract cancers of all four studies is impressive. Moreover, our study had adequate power (80%) to detect a 2-fold excess of lung cancer among all formaldehyde workers, and a 2.9-fold excess among workers continuously exposed above 0.1 ppm.

## III. Interpretation of the Findings

a) NIOSH comment:

". . . We do not believe a study as statistically weak as this should be used to support the position that an exposure of 1 ppm TWA with a 2 ppm ceiling is safe."

Du Pont response:

The power of the study has previously been addressed and need not be repeated.

NIOSH has obviously misinterpreted Du Pont's reliance on the study, concluding that we relied upon it as the sole support for our internal exposure level of 1 ppm TWA with a 2 ppm ceiling (measured over a 15-minute time period). In determining this Acceptable

Exposure Level (AEL), Du Pont considered all available health data — epidemiology, animal studies, and in-vitro testing. The Du Pont epidemiologic data were only one of many factors considered.

The Du Pont AEL for formaldehyde was established in January, 1981, to prevent irritation of exposed employees. Both Du Pont's Haskell Laboratory and Medical Division had also reviewed the animal toxicity data from the CIIT study on formaldehyde and the epidemiology studies which were described at the CIIT Conference on Formaldehyde of November 20-21, 1980.

In the CIIT 2-year rat and mouse inhalation study, nasal tumors were detected in rats (95/220) and mice (2/85) at 15 ppm and in rats (3/204) at 6 ppm. No nasal tumors were seen in rats and mice exposed to 2 ppm, or mice exposed to 6 ppm or in the unexposed controls. Nasal tissue damage, rhinitis, epithelial dysplasia, and squamous metaplasia were seen in rats at all levels of exposure, but the severity and extent of damage were dose related.

In a Formaldehyde Institute subchronic inhalation study, rats, monkeys, and hamsters were exposed to 3, 1, and 0.2 ppm, 22 hours every day for 6 months. Preliminary results showed that squamous cell metaplasia, a cell type change, occurred in nasal passages of rats and monkeys only at 3 ppm. The significance of this result is not clear in relationship to tumor development or for man.

Three epidemiological studies investigating cancer incidence of persons occupationally exposed to formaldehyde were presented at the CIIT Conference. Two of the studies dealt with chemical workers and one with morticians. No overall excess of cancers was found. However, a statistically significant increase in skin cancers was observed in the study involving morticians. No increase in nasal cancer or respiratory tract cancer was found.

Based on the results of the CIIT animal study, we concluded that formaldehyde causes nasal tumors in rats and mice by the inhalation route of exposure at concentrations which also produced cellular changes to the target tissue of the test animals. A comparison of the concentrations of formaldehyde that caused tumors in the CIIT study with concentrations of several other chemicals that produce similar tumors in animals suggests that formaldehyde possesses low to intermediate potency for producing nasal tumors in animals.

The relationship and significance of the results from the animal studies to man, in regard to cancer risk of persons exposed to formaldehyde, is not clearly known, but the lack of an excess of cancer reported from the epidemiology studies suggests the risk, if any, for man is low.

Based upon the information discussed above, we concluded that formaldehyde will not present a significant carcinogenic risk for man if appropriate exposure limits and good industrial hygiene practices are followed.

Pursuant to this determination, Du Pont issued guidance for limiting worker exposure to an 8-hour TWA of 1 ppm with a ceiling of 2 ppm.

The recently completed epidemiologic study of cancer mortality among Du Pont formaldehyde workers did not show an excess of cancer deaths in persons occupationally exposed to formaldehyde. As stated, in the study and transmittal letter, this finding provides further support to our conclusion that airborne levels of 1 ppm time-weighted average and a 2 ppm ceiling provide adequate employee protection.

b) NIOSH comment:

"In the last paragraph on page 18, the paper states, "We believe that the slight elevations in the prostatic and bladder cancer odds ratios are chance occurrences and are unrelated to the workers' exposure to formaldehyde." We disagree; it is possible that these elevations are not a result of formaldehyde exposure, but it seems less likely that these findings are due to chance. All of the exposure analyses presented suggested a dose-response trend for these sites. These findings, particularly for prostatic cancer, are consistent with other studies in the chemical industry. Marsh's study showed a significant (p less than .05) excess (PMR = 196) of prostatic cancer, and a suggestive excess of bladder cancer (2 observed, 0 expected). Wong's study also revealed a statistically significant (p less than .05) excess (SMR = 431) of prostatic cancer in workers with greater than 20 years of latency."

Du Pont response:

There were no statistically significant dose-response trends for prostate and bladder when these sites were examined by continuous/intermittent status, exposure level, duration of exposure, or cumulative exposure index.

We believe NIOSH has misinterpreted Marsh's study. The excess of prostatic cancer (PMR = 196) occurs in the group that was not exposed to formaldehyde (see Table 3 of Marsh's report). Marsh states that "the excess genito-urinary cancers observed in earlier studies of this plant appear to be concentrated in the non-formaldehyde group." Only 1 prostate cancer was observed in Marsh's formaldehyde cohort. Moreover, although there were 2 bladder cancer deaths in the Marsh study, 0.6 were expected, not 0.

Thus, the only other study reporting a slight excess for prostate was the Wong study. Our reasons (given in our report p.19) for discounting a causal relationship between formaldehyde exposure and prostatic cancer are repeated here for the convenience of NIOSH.

- The data suggest that by chance the controls chosen for prostate cases were not representative of the underlying control population with respect to formaldehyde exposure. The slight excesses observed for prostate appear to be due to under-representation of exposure in controls, not over-representation of exposure in cases.

  For example, only 9% of the prostate's controls were exposed whereas 20% of all controls were exposed. The exposure distribution for prostate cases, on the other hand, was similar to that found for all cancer cases and for their controls. Twenty-four percent of prostate cases were exposed vs. 21% of all cancer cases.

- Neither the Walrath nor the Marsh study showed an elevated risk for either cancer of the prostate or bladder.

- Our analyses assumed latent periods that were designed to maximize the observed relative risk ratios. This treatment of latent period may have tended to overestimate the true relative risk.

- The elevations in risk were based on small numbers of cases and were subject to considerable statistical variability. Even so, all of the odds ratios were within the limits of sampling variation and were consistent with a true odds ratio of 1.0.

- The prostate cases came from 6 plants, the bladder cases from 5 plants. No one plant showed risks that were particularly higher than the others even though past formaldehyde levels were higher in some plants than in others.

- Prostate and bladder cancers are biologically unlikely sites for the action of formaldehyde, given that the target site in animal studies was restricted to the upper respiratory tract, specifically the nasal cavity.

- The study was subject to the multiple comparison problem and should be interpreted accordingly. That is, any epidemiologic study of this size presents the investigator with a multitude of possible comparisons. A long series of comparisons will, with high probability, result in some comparisons testing significant, even in the absence of any causal relationships.

  In this study the probability that at least one comparison would show a significant difference simply on the basis of chance was better than 40%.

## IV. Study Design

### a) NIOSH comment:

"A major problem with this study's design is that in addition to formaldehyde, exposure to other carcinogens may have occurred. The list of carcinogens in Appendix C includes many potential respiratory carcinogens such as asbestos, chromates, and acrylonitrile.

As the authors suggest on page 17, if workers not exposed to formaldehyde were exposed to other carcinogens, this could mask the effects of formaldehyde. However, this study failed to try to account for the influence of these exposures on the study outcome. Perhaps a distribution of cases and controls exposed to these other agents could have been presented."

Du Pont response:

A great deal of time and effort has already gone into determining which study subjects have been exposed to formaldehyde and to what levels they have been exposed. To characterize study subjects' exposures according to all other potentially hazardous materials in the workplace would have required an inordinate amount of time and effort, if even feasible, and was considered to be beyond the scope of this study. In most occupational epidemiology studies of this type (including the Wong, Marsh, and Walrath studies), you will find that workers are exposed to chemicals in addition to the chemical of interest. The investigator wishing to learn more about the potential risks of a material is faced with a choice. He can do nothing, or he can do a study with the realization that the exposures to other materials could mask or inflate the true risk of the study material itself. We proceeded under the assumption that formaldehyde and nonformaldehyde workers were equally likely to have been exposed to other hazardous materials. We had no evidence to assume otherwise.

b) NIOSH comment:

"This paper should indicate the eligibility criteria for receiving death benefits from the Company's life insurance plan. Deaths covering this plan constituted the pool from which cancer cases in this study were selected. It is possible that these eligibility requirements may have eliminated greater than the estimated (page 16) 15-20% of the underlying workforce. This might have resulted in a serious negative bias if workers that were more sensitive to the effects of formaldehyde left the industry prior to meeting the eligibility requirements."

Du Pont response:

Until 1972, an employee had to have one year of service to be eligible for the life insurance plan. Since then, employees have been covered from the first day of employment. The entire premium is paid by the Company and coverage among employees is complete. Since coverage under the life insurance plan continues after an employee retires on a Company pension, all deaths among active and pensioned employees were included in the study.

From Du Pont's experience with cohort studies, we have found that about 15-20% of any given cohort will leave the Company prior to pensioning. For instance, in our study of the Louisville, Kentucky, chloroprene workers, 15% (243 of 1576) of the workers left without a pension and were therefore lost to follow-up through the Company's life insurance plan. Thirteen percent of the deaths in this total cohort occurred among the 243 who left without a pension. The mortality rate in those who left without a pension was no higher than the mortality rate in those who stayed with the Company.

Thus, we are confident that the formaldehyde study's design did not eliminate more than 15 to 20% of the underlying work force. For your convenience, the study's statements regarding nonpensioned terminations and transfers is repeated below:

> "Cancer deaths among employees who left the Company without a pension or who transferred to a plant not in the study were not included in the study. These exclusions might comprise about 15-20% of the underlying work force. The exclusion of these subjects would bias the results only if the reasons for leaving the plant were related both to past exposures and to the risk of dying from cancer. Even if these conditions were met, the extent of the bias was most likely minimal. A quantitative analysis of this situation showed that cancer risks in formaldehyde workers excluded from the study would have to be 5 to 10 times higher than the risk in those included before there would be a noticeable effect on the study's results. In short, it is unlikely that the exclusion of nonpensioned terminations and transfers could account for the study's negative findings."

## V. Other Issues

### a) NIOSH comment:

"Should not the possible confounding influence of race have been studied. For example, prostatic cancer rates differ sharply between blacks and whites."

Du Pont response:

The decision was made not to match or adjust for race because:

- 98-99% of the underlying employee populations were white, so that the confounding potential of race was extremely low. In fact, of all cases and controls (962), there were only 4 cases and 7 controls that were black (1.1%).
- Race would only have been a confounder if it had been related both to exposure status and disease, which we considered to be unlikely.

b) NIOSH comment:

"Table XII has an apparent error. 491 controls are listed in the All Sites category. However, there are only supposed to be 481 controls in the study."

Du Pont response:

Table XII does have a typographical error in the size of the All Sites control group having no exposure. The number in this group should be 377, not 387 as typed. With this correction, the total number of controls in Table XII adds to 481.

c) NIOSH comment:

"The report would have been more complete and easier to evaluate if the numbers of concordant and discordant case control pairs were included in each table."

Du Pont response:

This comment was answered previously.

## VI. Summary

a) NIOSH comment:

"We believe the study is limited by the analytic methods used, the study design, and the low statistical power, particularly for upper respiratory cancers (e.g., nasal). In view of these concerns, we do not believe the findings should be interpreted as the authors have suggested that airborne levels of 1 ppm TWA and a 2 ppm ceiling provide adequate worker protection."

Du Pont response:

The analytical method which was used represents the present state-of-the-art for this type of study; the study design is one of the most appropriate, as agreed to by NIOSH for the data which is available; and the statistical power is adequate, especially for cancer of the lung and bronchus. Nasal cancer is so rare that few study sizes or designs would have very great statistical power for this cancer site. The fact that no nasal cancers occurred in the study group is, however, very important.

As noted previously, the findings of this study were not the single criterion upon which we relied to conclude that airborne levels of 1 ppm TWA and a 2 ppm ceiling provide adequate worker protection. The findings of this study were, however, considered to "support" the previously established position that airborne formaldehyde levels of 1 ppm TWA and a 2 ppm ceiling provide adequate worker protection.

BWK:ceb
8/24/82

Reference:

(1) Rothman, K. J. "Induction and Latent Periods." American Journal of Epidemiology, Vol. 114, No. 2., pg. 253-259, 1981.

COMMITTEE ON SCIENCE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES
WASHINGTON, D.C. 20515

November 2, 1982

MEMORANDUM

TO: Robert B. Nicholas, Chief Counsel/Staff Director
Subcommittee on Investigations and Oversight

FROM: Phil Sokolove, Congressional Fellow PS

SUBJ: NCI Evaluation of DuPont Formaldehyde Study

At your request, I have reviewed the NCI and NIOSH evaluations of the DuPont Formaldehyde Study. Without the actual study data, it is difficult to comment meaningfully on the evaluation. However, certain points seem relatively clear.

1. DuPont apparently went to a lot of time and expense to conduct this study, and apparently attempted to carry it out without bias.

2. The results of the study failed to show a statistically significant risk increase for any form of cancer for exposed workers. (The evaluation does not dispute this finding and, in fact, commends the statistical methods used to conduct the analyses).

   This is really the bottom line, and it is not being questioned.

3. With one exception the "weaknesses" listed probably would not change the overall conclusion if they were to be corrected.

4. The major problem in my opinion is that the study could not be expected to yield a positive result (statistically speaking) except in the case of the lung. I cannot tell from the review whether this lack of "adequate statistical power" arises from a too-small data base or from improper study design. I suspect it is mainly the former.

   Because of this weakness the best one could expect in terms of a positive result would be only a trend toward increased risk for one or more sites. For this reason perhaps the results cited for prostate and bladder cancer ought to be weighed somewhat more heavily than they might otherwise be.

In sum I agree with the reviewers that while interesting, the results can at best be considered only preliminary at this point since the study could not have detected low to moderate increases in risk for most sites. Again, we have a case where the study has provided inconclusive, rather than "negative" results.

# APPENDIX 10

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Critique of Materials from S. John Byington,
Counsel for the Formaldehyde Institute

FROM: Joseph J. Merenda, Director
Assessment Division (TS-778)

TO: Warren R. Muir, Deputy Assistant
Administrator for Toxic Substances (TS-792)

The contents of the letter from S. John Byington, Counsel for the Formaldehyde Institute, appear to address two major subject areas: a) the adequacy of the technical evaluation of available data on formaldehyde; and b) sufficiency of the available data for making a 4(f) determination. The attached critique, thus, is divided into two sections. The first section identifies and addresses specific comments on the technical evaluation; the second addresses the major issues concerning the sufficiency of the available data for making a 4(f) determination.

Please let me know if this analysis satisfies your needs or if you need additional information.

## Adequacy of the Technical Evaluation

Mr. Byington's letter questions the soundness of some of the scientific analyses presented for the Administrator's consideration in making a decision on the applicability of TSCA, Section 4(f) to risks associated with formaldehyde exposures. The major technical issues raised by Mr. Byington are addressed below.

Issue #1: The only positive animal data that exist are still preliminary and must be considered in context with the other final animal data which do not show potential human carcinogenicity.

The positive data to which Mr. Byington refers come from a study conducted by the Chemical Industry Institute of Toxicology (CIIT). Since the CIIT final report is as yet unpublished (although one year has passed since the terminal sacrifice carried out June 4, 1980) the statement that the data are preliminary is technically correct. However, the fact remains that significant numbers of exposed animals developed tumors that were diagnosed as nasal squamous cell carcinomas by several independent groups. The CIIT pathologists overseeing the study, the Battelle Columbus Laboratory pathologists conducting the experiment, and a group of independent pathologists sponsored by the Interagency Regulatory Liaison Group (IRLG) Taskgroup on Formaldehyde have all agreed that 36 nasal squamous cell carcinomas were evident in animals sacrificed and examined at the 18-month point of the two-year study.

Nasal squamous cell carcinomas are extremely rare in the type of animals used in the CIIT bioassay (Fisher 344 rats). In fact, the National Cancer Institute, in a letter to OSHA, reported that only two cases of this type of cancer had been observed in over 4000 Fisher 344 rats examined. The CIIT pathologists, in examining several thousand aging Fisher 344 rats, have never found this type of cancer. Viewed from this perspective, 36 animals developing this type of cancer (out of a total of 2 exposed) indicates cause for concern. The need for serious concern became even more apparent when data became available for the terminal sacrifice (those animals surviving the full 24 months). Considering both the interim and terminal sacrifices a total of 95 rats in the high dose (14.1 ppm formaldehyde) group and 3 rats in the intermediate dose (5.6 ppm formaldehyde) group were found to have nasal carcinomas (information presented at the November 1980 CIIT Conference on Formaldehyde Toxicity by Drs. Swenberg and Kerns of CIIT and Battelle, respectively).

[illegible]

Thus, although the CIIT data are preliminary insofar as a final report has yet to be released, there is scientific agreement that a significant number of rare cancerous tumors were found in experimental animals as a direct result of formaldehyde exposures at the high and intermediate doses. The fact that no such tumors were reported for the low dose (2.1 ppm formaldehyde) group should not be taken as evidence that lower exposures do not present a cancer risk; current scientific thinking does not accept a "no effect level" for cancer, simply reduced risk at lower exposures which is accounted for in cancer risk models used by EPA and others.

from wh.

In response to Mr. Byington's suggestion that final animal data which do not show potential human carcinogenicity must be considered, the Agency, in its PRL-1 assessment (pages 84-85), did consider two inhalation studies and three feeding studies in which it appears that exposure to formaldehyde did not result in tumor development. There are major flaws in the inhalation studies: (a) the noses of the exposed animals were not systematically examined for the presence of tumors; and (b) the numbers of animals used in these experiments were small. In the feeding studies, hexamethylenetetramine (HMT) was fed to animals. When HMT is fed, it breaks down to produce ammonia and formaldehyde under the acidic conditions usually observed in the stomach and kidneys. In the studies mentioned in the PRL-I (pages 87-88), neither the rate of formaldehyde release, the levels generated, nor the influence of food in the stomach is known, making it difficult to assess the carcinogenic effects of formaldehyde administered by this means.

Finally, in the same statement (page two, paragraph three) Mr. Byington intimates that the CIIT study has received only one peer review. It is true that only one peer-reviewed journal article has been published on the CIIT bioassay. However, the pertinent data and experimental design of the CIIT study were carefully evaluated by (a) the Federal Formaldehyde Panel convened by CPSC under the auspices of the National Toxicology Program; (b) scientists at the Environmental Cancer Information Center of the Mt. Sinai Medical Center in New York; and, (c) the scientists at NIOSH, OSHA, and EPA. All of these groups concluded that the CIIT bioassay met accepted standards for tests designed to evaluate the carcinogenicity of chemicals delivered via inhalation. Further, the Federal Panel on Formaldehyde, whose carcinogenicity review was used extensively in the preparation of EPA's PRL-I assessment, and the group at the Mt. Sinai Medical Center emphasized that cancers occurred in animals at levels (5.6 ppm) not unlike those which can be found in human exposures.

Issue #2: Your staff buttresses the CIIT study with the results of an unpublished New York University study that is now being repeated due to lack of controls.

Attachment C to Mr. Byington's letter (a letter from Dr. Demopoulos of NYU Medical Center to James Remay of the Formaldehyde Institute) specifically refers to the study of Laskin et al. The PRL-1 report presents the details of this study, but addresses the study with qualifications regarding its interpretation. Specifically, the PRL-1 report states: "suggestive evidence for the carcinogenicity of inhaled formaldehyde vapors also comes from a study by Laskin et al (see page 83). "While the results suggest that formaldehyde (rather than BCME) is the major etiological agent in this experiment, considerable uncertainty remains, and other interpretations are possible" (see page 84).

As reported in the PRL-1, animals in the Laskin et al. study were exposed to formaldehyde and hydrogen chloride gas in combination, which results in the formation of bis(chloromethyl)ether (BCME), a potent carcinogen. When 27% of the exposed rats developed nasal squamous cell carcinomas the authors believed that there was a strong possibility that formaldehyde was the etiological agent. This was explained by the fact that the BCME level was too low to be expected to cause this frequency of cancer, and that the nasal squamous epithelial tumors found in the treated animals differed morphologically from esthesioneuroepitheliomas that typically occur in rats exposed to BCME.

This study currently is being repeated, with appropriate controls, by Dr. Sellakamur of NYU Medical Center; it is in the 72nd week of a scheduled lifetime (104 week) study. In a May 28 telephone conversation with Dr. Sellakamur,* he stated that 4 nasal squamous cell carcinomas have been detected among 17 rats (unscheduled deaths) exposed to formaldehyde alone at 15 ppm. These results, however, are extremely preliminary and, any conclusion regarding the value of the original study by Laskin et al. will have to await completion of the bioassay being conducted by Sellakamur.

In summary, we agree with Mr. Byington that the Laskin (NYU) study suffered from substantial experimental design weaknesses. The results of this study (and preliminary data from NYU's followup study) do show the same link between formaldehyde exposure and nasal squamous cell cancer in rats that was clearly evident in the CIIT study. Nevertheless we consider the Laskin study data to be merely "suggestive" as stated in the PRL-1 assessment.

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*Written confirmation is forthcoming.

Issue #3: Negative animal chronic testing data which have not been considered by EPA staff demonstrate the need for additional studies in order to understand the implications, if any, for humans of the CIIT results.

As discussed under Issue #1, the EPA staff did consider in the PRL-1 report a number of studies that, rather than being considered "negative", should more correctly be termed "inconclusive". EPA is not aware of other chronic studies on formaldehyde which reasonably can be considered as adequate animal bioassays for carcinogenicity.

Issue #4: Little, if any emphasis has been given to the fact that the four epidemiology studies to date have negative.

In fact, ten pages of the PRL-1 report (Appendix A, pages 120-130) are devoted to a discussion of proposed, ongoing and completed epidemiology studies. Of the studies considered to be negative by Mr. Byington (supplied in Attachment D to his letter), one of these studies (Walrath et al.) suggests an increase in cancers of skin, kidney and brain in morticians. In two other studies involving formaldehyde workers, the study populations (the number of deaths) examined were 136 (Wong et al.) and 132 (Marsh). These sample sizes are far too small to allow any conclusive assessment of the carcinogenicity or non-carcinogenicity for formaldehyde. In addition, not enough time was allowed for potential cancers to develop; nor was it known how many of the persons studied were exposed to formaldehyde, at what concentrations of exposure and for how long. The same inadequacies also apply to the study by Harrington and Shannon addressed in Attachment D to Mr. Byington's letter. Thus, these studies are incomplete and generally lack the ability to detect increases in cancer rates that would, nevertheless, be significant considering the widespread exposure to formaldehyde. Therefore, they should not be cited as evidence that formaldehyde is not carcinogenic in humans.

## Sufficiency of Available Data for Making a 4(f) Determination

There appear to be three major issues developed in Mr. Byington's letter with respect to whether the available data on formaldehyde's carcinogenic potential are sufficient to make a TSCA section 4(f) determination: 1) the CIIT bioassay results are preliminary results that have not been published; 2) there is an absence of positive epidemiology studies to support the presumption that formaldehyde is a human carcinogen; and 3) there is insufficient information to make the requisite finding that there may be a reasonable basis to conclude that formaldehyde presents a significant risk of serious or widespread harm. Each of these issues is discussed below.

### Issue #1: Preliminary Bioassay Results that are not Published

The PRL-1 report states many times that the results of the CIIT carcinogen bioassay are preliminary (see for example pages viii, 1, and 82), and emphasizes that the risk estimates should be interpreted cautiously for a number of reasons including, "the number provided for animals with tumors and for total animals at risk may change when the final histopathology and experimental analyses are completed by the CIIT" (see page 91). Although the PRL-1 emphasizes the preliminary nature of the CIIT bioassay data, it does not address the question of whether EPA should use such data to make a TSCA section 4(f) decision.

page 83). "While the results suggest that formaldehyde (rather than BCME) is the major etiological agent in this experiment, considerable uncertainty remains, and other interpretations are possible" (see page 84).

As reported in the PRL-1, animals in the Laskin et al. study were exposed to formaldehyde and hydrogen chloride gas in combination, which results in the formation of bis(chloromethyl)ether (BCME), a potent carcinogen. When 27% of the exposed rats developed nasal squamous cell carcinomas the authors believed that there was a strong possibility that formaldehyde was the etiological agent. This was explained by the fact that the BCME level was too low to be expected to cause this frequency of cancer, and that the nasal squamous epithelial tumors found in the treated animals differed morphologically from esthesioneuroepitheliomas that typically occur in rats exposed to BCME.

This study currently is being repeated, with appropriate controls, by Dr. Sellakamur of NYU Medical Center; it is in the 72nd week of a scheduled lifetime (104 week) study. In a May 28 telephone conversation with Dr. Sellakamur,* he stated that 4 nasal squamous cell carcinomas have been detected among 17 rats (unscheduled deaths) exposed to formaldehyde alone at 15 ppm. These results, however, are extremely preliminary and, any conclusion regarding the value of the original study by Laskin et al. will have to await completion of the bioassay being conducted by Sellakamur.

In summary, we agree with Mr. Byington that the Laskin (NYU) study suffered from substantial experimental design weaknesses. The results of this study (and preliminary data from NYU's

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*Written confirmation is forthcoming.

The only precedent for addressing the question of when the Agency will use other than final, published bioassay results is found in the Agency's response to a Section 21 Petition on DEHP, where the use of a preliminary NCI bioassay was discussed. That response states, in part:

> In general, EPA considers it necessary to await the availability of final, publicly reviewed results from the NCI bioassay program before using such data to make regulatory decisions dependent on the degree of risk posed by a chemical. This includes the types of decisions made under section 4(f) of TSCA. However, the Agency also believes that data available at earlier stages of NCI's verification and review process may be adequate in some cases to make qualitative judgments as to the chemical's carcinogenic potential. EPA will use preliminary data (from NCI or other sources) for this purpose where EPA scientific review of the available data indicates that the qualitative determination is quite clear-cut and, especially, where an Agency decision must be made before more fully reviewed data will be available....

As discussed in the PRL-1 report and above, the preliminary results of the CIIT bioassay have been reviewed not only by OTS staff scientists, but also by a panel of experts convened under the aegis of the National Toxicology Program (NTP). The NTP panel also reviewed the method of formaldehyde generation and monitoring used in the CIIT study and agreed that "the Battelle approach to formaldehyde vapor generation was a suitable adaptation of accepted methods and principles and, therefore, was sound and based upon the best available technology." The same type of assessment applied to the chamber air monitoring system, which also combined two well-established procedures (PRL-1, page 83). Both the OTS scientists and the NTP panel concluded that formaldehyde is a carcinogen in rats. The NTP panel report also concludes that "formaldehyde poses a cancer risk to humans."

Why mention again since CPSC panel reviewed only histology

In addition to these evaluations, a memorandum released on April 30, 1981, by the Consumer Product Safety Commission states that "scientists at the Environmental Cancer Information Center of the Mt. Sinai Medical Center in New York, the scientists at the CIIT,

Why not [illegible] [illegible] CPSC [illegible] not true

and the scientists at NIOSH and OSHA have concluded that formaldehyde is indeed an animal carcinogen. The Federal Panel on Formaldehyde and the group at the Mt. Sinai Medical Center further emphasized that the cancers occurred in animals at levels not unlike those which can be found in human exposures."

Given the large number of scientists and institutions that have concluded that formaldehyde is an animal carcinogen based on the preliminary CIIT bioassay results, one can argue that the study has received considerable public review and that the weight of scientific opinion, based on currently available information, clearly supports the Agency's adopting a position that formaldehyde is an animal carcinogen. A major factor in deciding whether formaldehyde poses a cancer hazard (or risk) to humans, however, centers on the question of whether confirmatory epidemiology studies are needed before such a determination can be made.

Issue #2: Lack of Positive Epidemiology Studies

The central question in considering this issue is not whether a definitive epidemiology study exists (one does not), but whether epidemiologic evidence is needed before one can consider that an agent represents a carcinogenic hazard (or risk) to humans. With respect to this question there are two position statements that should be considered. The first is the EPA Interim Cancer Assessment Procedures (released May 19, 1976) which state:

> ...in very few cases is it possible to prove that a substance will cause cancer in man, because in most instances the evidence is limited to animal studies. In this regard, a substance will be considered a presumptive cancer risk when it causes a statistically significant excess incidence of benign or malignant tumors in humans or animals.

The second is the more recent, final Risk Assessment Report of the Interagency Regulatory Liaison Group (IRLG) released February 6, 1979. This report states the following in regard to considering available epidemiology studies in evaluating carcinogenic risks:

> Absence of a positive statistical correlation does not by itself demonstrate absence of a hazard. While negative epidemiologic data usually do not adequately establish the non-carcinogenicity of suspected materials, such negative data on a given agent obtained from epidemiologic studies of sufficient extent and duration may be useful for indicating upper limits for the rate at which a specific type of exposure could affect the incidence and/or mortality of specific human cancers, under the conditions of observation.

On the basis of the above statements, one can reasonably conclude that confirmatory epidemiologic studies are not essential to concluding that a substance presents a (presumptive) cancer risk to humans, if available data demonstrate that the substance is an animal carcinogen. Assuming that one accepts this argument, as well as the argument that it is appropriate to use the CIIT preliminary bioassay results in evaluating the carcinogenicity of formaldehyde, the remaining issue is whether the available information is sufficient to conclude that formaldehyde may pose a significant risk of serious or widespread harm.

Issue #3: Sufficiency of the Available Data for Supporting the Section 4(f) Finding

This issue can be considered most easily by subdividing it into two topics: a) definitions of significant risk, serious, and widespread; and b) how certain EPA must be that a chemical poses a significant risk of serious or widespread harm before designating the chemical for priority attention under Section 4(f). The only documented positions that have been developed on these issues appear in a memorandum prepared by David Menotti and Steve Atkinson of EPA's Office of General Counsel.*

With respect to the definitions of significant risk, serious, and widespread, the above memorandum states:

> The term "significant risk" is neither defined in the Act nor discussed into the legislative history. Generally, "significance" is a term which is used to refer to the likelihood that a certain harm will in fact occur. However, there is no clear standard as to when a chance of injury is significant and when it is not, although general agreement might be reached as to the extremes on either side....Congress also failed to define the terms "serious" and "widespread" or to discuss how it intended the terms to be applied in a Section 4(f) context. However, the terms "serious and widespread" are also utilized in Section 7(f) of TSCA as part of the definition of "imminently hazardous chemical substances" against which EPA may seek injunctive relief. With reference to Section 7, the conferees indicated that "widespread injury" was intended to refer to a "risk affecting a substantial number of people." The term "serious" was distinguished from widespread by the fact that to be "serious" a risk need not affect a substantial number of persons.

If one accepts these definitions, he/she can reasonably conclude that exposure to formaldehyde may result in widespread cancer risk. In excess of 4,700,000 individuals are estimated to be exposed to non-trivial concentrations of formaldehyde (see Table 7, pages 56-59 of the PRL-1).** A determination of whether the

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*Subject: Primer on TSCA Section 4(f); To: Steven Jellinek, Assistant Administrator for Pesticides and Toxic Substances; Date: October 30, 1980. This memorandum was released as an attachment to the Agency's response to a Section 21 Petition on DEHP.

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risks are significant, however, involves a consideration of the actual levels of formaldehyde to which various subpopulations are exposed, as well as any differences between the manner in which humans and rats handle exposures to formaldehyde.

Once formaldehyde enters the body, through various routes of exposure including inhalation, it appears to be metabolized by the same pathways in all mammalian species examined to date, although reaction rates differ among various species and tissues (PRL-1, page 81). A major difference between humans and rats, however, is that rats are obligatory nose breathers while humans are not (PRL-1, page 92). To the extent that the carcinogenic response in rats is a result of continual inflammation of the nasal passages (because they are obligatory nose breathers), the nature (e.g., the site) and extent of the carcinogenic response in rats may differ from that in humans (although humans also may be partial nose breathers). The available evidence, however, is sufficient to neither support nor refute the role of inflammation in the development carcinomas of the nasal epithelium in rats exposed to formaldehyde. CIIT, currently is conducting experiments that may provide additional information on this point.

These are not arguments about the mechanism, i.e. whether [illegible] is relevant in man?

Likewise, one cannot rule out the possibility that formaldehyde carcinogenesis is a cellular event, since positive results in numerous short-term tests for mutagenic activity clearly indicate that formaldehyde interacts with DNA. Formaldehyde produces gene mutations in bacteria and other eukaryotic microorganisms and, in higher organisms, chromosomal aberrations such as deficiencies, duplications, inversions and translocations. Formaldehyde also has been shown to interact with other known mutagens and to at least double the expected frequency of mutants. Although the PRL-1 report does not attempt to develop the available information on formaldehyde's mutagenic potential in support of a carcinogensis bioassay, the final IRLG Risk Assessment Report (released February 6, 1979) states with respect to short-term tests in the study of carcinogenesis at the cellular level:

> Short-term tests for chemical carcinogens presently do not, in the absence of animal bioassay and epidemiology data, constitute definitive evidence as to whether a substance does (or does not) pose a carcinogenic hazard to humans. However, positive responses in these tests are considered suggestive evidence of a carcinogenic hazard. Positive results from these tests also supply supporting evidence to positive animal bioassay or epidemiology results.....

The available data, thus, indicate that formaldehyde is a carcinogen, but do not enable one to define its mechanism of carcinogenesis (i.e., cellular or inflammatory). In the absence of information to define the mechanism by which formaldehyde causes cancer in rats, and in the absence of any definitive evidence which demonstrates that it does not cause cancer in humans, there is no scientifically valid basis for concluding that formaldehyde will not be a human carcinogen.

With respect to how certain the Administrator must be that a chemical poses a significant risk of serious or widespread harm from cancer, birth defects, or gene mutations before designating the chemical for priority attention under Section 4(f), the memorandum prepared by EPA's Office of General Counsel states the following.

> Section 4(f) states that EPA must designate a chemical as a priority candidate when information indicates that there "may be a reasonable basis" to find that a high degree of risk exists from cancer, birth defects, or gene mutations. In contrast, the regulatory authorities provided by TSCA under Sections 5, 6, and 7 generally require EPA or a federal court to find that there "is a reasonable basis to conclude" that an unreasonable risk to health or the environment is presented.
>
> It follows from the difference in language that a 4(f) designation requires less certainty as to the existence of a particular level of risk than the major regulatory

> provisions of TSCA require with respect to a finding of "unreasonable risk." This distinction is consistent with the different purposes served by these provisions. Section 4(f) designates candidates for expedited regulatory decisionmaking, and itself imposes no regulatory controls. Instead, it triggers a period of intensive study on whether the Agency should initiate action to control the substance; initiation is only the first step in a process which may eventually lead to promulgation of a regulation.

In the case of the risks associated with exposures to formaldehyde, the certainty of the risk estimates in the PRL-1 report is strongly influenced by the quality of the available exposure data as well as any confounding factors surrounding the CIIT bioassay and its use in estimating carcinogenic risks to humans. As discussed in the exposure assessment of the PRL-1 report "much of the available exposure data may not be representative of the levels of formaldehyde to which various subpopulations are routinely or continuously exposed. Formaldehyde levels in the workplace, for example, are based on monitoring data for only a few plants in some instances and, in some of the monitoring studies, for only one or a few locations in the plant. Likewise, the available exposure data involving consumer situations (e.g., mobile homes) may be representative of worst case situations rather than the average exposure, if one assumes that there is a tendency to monitor primarily those homes identified through consumer complaints" (see page 92 of PRL-1).

Although more extensive and more reliable information on the size of exposed populations and actual exposure levels is needed before one could determine the need for regulation of formaldehyde under section 6 of TSCA, the available data strongly suggest that a potentially large number of individuals are exposed to formaldehyde, with certain subpopulations being exposed to levels similar to, or slightly below, those that induce cancer in rats.

## Summary

On the basis of the above discussion and information presented in the PRL-1 report, the following facts might logically lead one to conclude that "there may be a reasonable basis to conclude that formaldehyde presents a significant risk of serious or widespead harm".

A) Although the results of the CIIT bioassay are preliminary, the bioassay protocol has been reviewed by a panel of experts convened under the aegis of the National Toxicology Program, and found to be consistent with accepted standards for conducting inhalation exposure bioassays.

B) Scientists within the Agency's Office of Toxic Substances and the NTP panel of experts, as well as a number of scientists in other institutes, have concluded that formaldehyde is a carcinogen in rats.

C) In the absence of data to the contrary, there does not appear to be a reasonable basis for one to conclude that formaldehyde does not pose a carcinogenic hazard (or risk) to humans. Agency and IRLG policies on the need for confirmatory epidemiology studies suggest that, while such studies can provide evidence that a substance is a human carcinogen, the absence of a positive correlation between cancer and human exposure to a substance does not in itself demonstrate absence of a hazard (or risk).

D) There is a reasonable expectation that a large number of individuals are being exposed to formaldehyde, with certain subpopulations being exposed to formaldehyde levels similar to, or slightly below, those found to induce cancer in rats.

E) Given the large number of individuals exposed, and the similarity between some of the estimated/known human exposure levels and those found to cause cancer in rats, there is a reasonable basis to expect that significant human cancer risks may be associated with these formaldehyde exposures.

# APPENDIX 11

## FORMALDEHYDE'S LOW DOSE CANCER RISK EXTRAPOLATION USING THE MULTISTAGE MODEL AND GLOBAL 79

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## I. Introduction

The potential carcinogenic effects of formaldehyde released from urea formaldehyde foam insulation (UFFI) have been recently assessed by the United States Consumer Product Safety Commission staff and reported in "Revised Carcinogenic Risk Assessment for Urea Formaldehyde Foam Insulation: Estimates of Cancer Risk Due to Inhalation of Formaldehyde Released by UFFI" by Murray S. Cohn. Obviously, a great deal of hard work has gone into this assessment. Of course, a number of choices and assumptions had to be made concerning the level of human exposure, the effects of an exposure level which tends to decrease over time, the extrapolation from rats to man, and the low dose risk extrapolation methodology to be applied to the animal data. Only the low dose extrapolation via the multistage model and the computer program GLOBAL 79 is discussed here. This discussion is particularly relevant to cases such as formaldehyde where the animal data provides no direct experimental evidence of carcinogenic risk at the lower experimental dose levels.

The Chemical Industry Institute of Toxicology (CIIT) study on rats exposed to formaldehyde will serve as a basis for our discussion of the empirical behavior of the multistage model analysis via GLOBAL 79. The distilled version of the CIIT study referred to in the CPSC report is reproduced in Table 1 which indicates the four experimental dose levels (0, 2.1, 5.6, and 14.1 ppm), the number (160) of rats at risk at each dose level, and the number of rats responding at each dose level (0, 0, 3, and 87 respectively).

Table 1. The Number of Rats Developing a Malignant Nasal Cancer in the CIIT Study of Rats Exposed to Formaldehyde

| | Dose Level (ppm) | | | |
|---|---|---|---|---|
| | 0 | 2.1 | 5.6 | 14.1 |
| Number at Risk | 160 | 160 | 160 | 160 |
| Number Developing a Malignant Nasal Cancer | 0 | 0 | 3 | 87 |
| Percentage Response | 0.0% | 0.0% | 1.875% | 54.375% |

## 2. The Multistage Model and GLOBAL 79

The multistage model for the probability of a "response" at dose d during the experiment is

$$P(d) = 1 - \exp\left[- (q_0 + q_1 d + q_2 d^2 + \ldots + q_K d^K)\right] \qquad (2.1)$$

where $q_0, q_1, \ldots, q_K$ are nonnegative constants. The definition of a "response" can be tumor onset, death due to a tumor, etc. and can specify the "response" site (such as liver, bladder, or either) as well as the severity of the response (such as hyperplasia, moderately well-differentiated carcinoma, a metastisizing tumor, etc.). The response of interest in the CIIT rats is malignant nasal cancer. Presumably there was no other carcinogenic response rate which increased at positive experimental dose levels.

The computer program GLOBAL 79, prepared by K.S. Crump and his associates, very efficiently determines the maximum likelihood estimates $\hat{q}_0, \hat{q}_1, \ldots, \hat{q}_K$ of the unknown nonnegative parameters $q_0, q_1, \ldots, q_K$ in the multistage model for a specified maximum degree K. The maximum likelihood estimate of the probability of a response at dose d is

$$\hat{P}(d) = 1 - \exp\left[-(\hat{q}_0 + \hat{q}_1 d + \ldots + \hat{q}_K d^K)\right] . \qquad (2.2)$$

The maximum likelihood estimate $\hat{P}(d)$ is referred to as the "best-fit-of-data estimate" in the CPSC report.

If $q_1$ is positive, then for small d the excess risk, P(d)-P(0), satisfies the approximation

$$P(d) - P(o) \doteq q_1 d \quad . \qquad (2.3)$$

Hence, GLOBAL 79 also determines an upper confidence limit on the linear parameter $q_1$ . Roughly speaking, the upper confidence limit $q_1^*$ on $q_1$ is the largest value of $q_1$ which is not inconsistent with the data. (See Crump (1981) for details.)

The maximum likelihood estimates $\hat{q}_0, \hat{q}_1, \ldots, \hat{q}_K$ are used to provide the maximum likelihood estimates of the risk P(d) and the excess risk P(d) - P(o) . The upper confidence limit $q_1^*$ is used to provide upper confidence limits on the excess risk P(d) - P(o).

## 3. GLOBAL 79's Limited Ability to Reflect Nonlinear Dose Response Relationships

The user of the multistage model (2.1) must specify the parameter K. Since some of the parameters $q_i$ in (2.1) may be zero, the specified value of K represents only an upper bound on the number of possible stages in the underlying multistage conception of cancer. In GLOBAL 79 the parameter K must satisfy the constraint that there should be no more parameters $(q_0, q_1, \ldots, q_K)$ in the model than there are dose groups; that is, K must be less than or equal to the number of dose groups minus one. Since there were 4 dose groups (0, 2.1, 5.6 and 14.1 ppm) in the CIIT experiment, K must be less than or equal to 3; that is, $K \leq 3$.

Often the upper bound on K is not very restrictive. However, when there is no direct experimental evidence of carcinogenic risk at the zero dose level and one or more of the smallest positive dose levels, then the upper bound on K may indeed limit GLOBAL 79's ability to fit the nonlinearity (flatness) of the dose response relationship in the low dose region including the lower experimental doses. This is the case with the CIIT formaldehyde data. Here there was no direct experimental evidence of carcinogenic risk at 0 ppm and 2.1 ppm.

Figure 1 indicates the inability of the multistage model with K = 3,

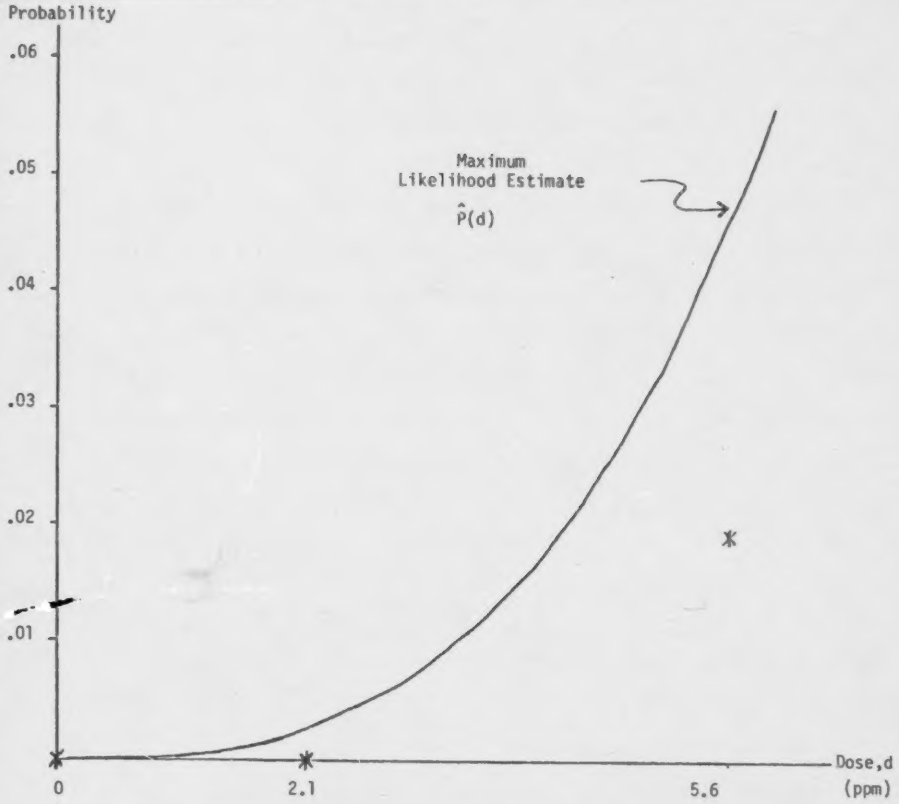
$$P(d) = 1 - \exp\left[-(q_0 + q_1 d + q_2 d^2 + q_3 d^3)\right] , \qquad (3.1)$$

to reflect the low dose nonlinearity in the experimental data. The maximum likelihood estimate of P(d) here i,

$$\hat{P}(d) = 1 - \exp\left[-.00026394d^3\right] \qquad (3.2)$$

where $\hat{q}_0$, $\hat{q}_1$, and $\hat{q}_2$ are all zero. Roughly speaking, Figure 1 shows that, when $K \leq 3$ (corresponding to only 4 dose levels), the maximum likelihood estimate of P(d) can't get down fast enough from an observed risk of 87/160 at 14.1 ppm to reflect the observed risks of 3/160 at 5.6 ppm and 0/160 at 2.1 ppm. With

Figure 1. A Plot of GLOBAL 79's Maximum Likelihood Estimates of Risk (Best-Fit-of-Data Estimates) versus the Observed Response Rates in the CIIT Rat Experiment



✱ = Observed Response Rate in CIIT Experiment

$K \leq 3$, the maximum likelihood estimate of P(d) at d = 5.6 is

$$\hat{P}(5.6) = 1 - \exp\left[-.00026394(5.6)^3\right]$$
$$\doteq .04529$$

as opposed to the observed risk

$$3/160 = .01875$$

Thus, when $K \leq 3$, the maximum likelihood estimate overestimates the observed risk at 5.6 ppm by a factor of 2.4 ,

$$.04529/.01875 \doteq 2.4155 \quad .$$

Two additional analyses were performed in order to further confirm that GLOBAL 79's maximum likelihood estimates of risk are being forced to overestimate the observed risks because of the limitation on K due to the number of dose levels in the CIIT experiment. In the first confirmatory analysis the original 160 rats at 2.1 ppm were split into two subgroups of 80 rats each. Of course, since none of the 160 rats at 2.1 ppm responded, the observed response rates for each of the two subgroups is 0/80. Now, if the dose levels for these two subgroups are taken as 2.05 and 2.15 instead of 2.1, then we have virtually the same experimental evidence, but there would be 5 dose levels (0, 2.05, 2.15, 5.6 and 14.3 ppm), and the limitation on K would be $K \leq 4$. The maximum likelihood estimate of P(d) under the less restrictive limitation, $K \leq 4$, is

$$\hat{P}(d) = 1 - \exp\left[-.00001982\ d^4\right] \tag{3.3}$$

where now $\hat{q}_0$, $\hat{q}_1$, and $\hat{q}_2$ are zero as before but also $\hat{q}_3 = 0$. With $K \leq 4$ , the maximum likelihood estimate of risk at 5.6 ppm is

$$\hat{P}(5.6) = 1 - \exp\left[-.00001982(5.6)^4\right]$$
$$\doteq .01930$$

which agrees very well with the observed response rate of .01875 at 5.6 ppm. In the second confirmatory analysis, the 160 rats at 2.1 ppm were split into 3 subgroups of 50, 60 and 50 rats. The observed response rates were taken to be 0/50, 0/60, and 0/50 at 2.05, 2.1 and 2.15 ppm respectively. As before, we have essentially the same experimental evidence but with 6 dose levels (0, 2.05, 2.1, 2.15, 5.6 and 14.3 ppm) and $K \leq 5$. When $K \leq 5$,

$$\hat{P}(d) = 1 - \exp\left[-(.0000180d^4 + .000000134d^5)\right] \qquad (3.4)$$

which is essentially the same model as (3.3) which was obtained when $K \leq 4$.

Table 2 indicates the maximum likelihood estimates of risk at the experimental dose levels 5.6 ppm and 2.1 ppm as well as several dose levels between 0 and 1 ppm. The estimates are shown for each of the 3 limitations $K \leq 3$, $K \leq 4$, and $K \leq 5$. The maximum likelihood estimate of the risk at the experimental dose level 5.6 ppm becomes closer to the observed rate (.01875) as the restriction on K is lessened from $K \leq 3$ to $K \leq 4$. Furthermore, the maximum likelihood estimates at the rest of the dose levels in Table 2 change considerably from $K \leq 3$ to $K \leq 4$. The changes from $K \leq 4$ to $K \leq 5$ are much less than those from $K \leq 3$ to $K \leq 4$. Thus, it appears that GLOBAL 79's maximum likelihood estimates of risk were significantly restricted by the number of dose levels in the CIIT experiment.

Another illustration of the limitation placed on GLOBAL 79's maximum likelihood estimates by the number of experimental dose levels is given in Table 3. There the maximum likelihood estimates are given for both the actual observed rates (0/160, 0/160, 3/160 and 87/160 at 0, 2.1, 5.6 and 14.1 ppm respectively) and the hypothetical rates (0/160, 0/160, 0/160 and 87/160 at 0, 2.1, 5.6, 14.1 ppm respectively) which differ dramatically at 5.6 ppm. One would have expected that the maximum likelihood estimates would have differed considerably in these two cases. In fact, the two sets of estimates are uncomfortably similar. The similarity is forced by the limitation on K implied by the number of experimental doses.

Table 2. The Limitation on the Multistage Model's Maximum Likelihood Estimate of Risk Due to the Number of Experimental Dose Levels

| Dose | Number of Exp. Dose Levels | | |
|---|---|---|---|
| | 4 ($K \le 3$) | 5 ($K \le 4$) | 6 ($K \le 5$) |
| .01 | .264(-9)* | .198(-12) | .180(-12) |
| .02 | .211(-8) | .317( 11) | .287(-11) |
| .03 | .713(-8) | .161(-10) | .146(-10) |
| .04 | .169(-7) | .507(-10) | .460(-10) |
| .05 | .330(-7) | .124(-9) | .112(-9) |
| .06 | .570(-7) | .257(-9) | .233(-9) |
| .07 | .905(-7) | .476(-9) | .432(-9) |
| .08 | .135(-6) | .812(-9) | .736(-9) |
| .09 | .192(-6) | .130(-8) | .118(-8) |
| .1 | .264(-6) | .198(-8) | .180(-8) |
| .2 | .211(-5) | .317(-7) | .288(-7) |
| .3 | .713(-5) | .161(-6) | .149(-6) |
| .4 | .169(-4) | .507(-6) | .461(-6) |
| .5 | .330(-4) | .124(-5) | .113(-5) |
| .6 | .570(-4) | .257(-5) | .234(-5) |
| .7 | .905(-4) | .476(-5) | .434(-5) |
| .8 | .135(-3) | .812(-5) | .740(-5) |
| .9 | .192(-3) | .130(-4) | .119(-4) |
| 1.0 | .264(-3) | .198(-4) | .181(-4) |
| 2.1 | .244(-2) | .385(-3) | .355(-3) |
| 5.6 | .453(-1) | .193(-1) | .182(-1) |
| 14.1 | .523 | .543 | .544 |

* The table entries are in scientific notation where, for example, .264(-9) = .000000000264.

Table 3. A Comparison of the Maximum Likelihood Estimates under the Restriction $K \leq 3$ for both the Observed Rates (with 3/160 at 5.6 ppm) and the Hypothetical Rates (with 0/160 at 5.6 ppm)

| Dose | 3/160 at 5.6ppm | 0/160 at 5.6ppm |
|---|---|---|
| .01 | .264(-9) | .255(-9) |
| .02 | .211(-8) | .204(-8) |
| .03 | .713(-8) | .687(-8) |
| .04 | .169(-7) | .163(-7) |
| .05 | .330(-7) | .318(-7) |
| .06 | .570(-7) | .550(-7) |
| .07 | .905(-7) | .873(-7) |
| .08 | .135(-6) | .130(-6) |
| .09 | .192(-6) | .186(-6) |
| .1 | .264(-6) | .255(-6) |
| .2 | .211(-5) | .204(-5) |
| .3 | .713(-5) | .687(-5) |
| .4 | .169(-4) | .163(-4) |
| .5 | .330(-4) | .318(-4) |
| .6 | .570(-4) | .550(-4) |
| .7 | .905(-4) | .873(-4) |
| .8 | .135(-3) | .130(-3) |
| .9 | .192(-3) | .186(-3) |
| 1.0 | .264(-3) | .255(-3) |
| 2.1 | .244(-2) | .235(-2) |
| 5.6 | .453(-1) | .437(-1) |
| 14.1 | .523 | .510 |

## 4. GLOBAL 79's 95% Upper Confidence Limits on Excess Risk

A 95% upper confidence limit on the excess risk, P(d)-P(0), at dose d is the result of a procedure which 95% of the time produces limits (numbers) which exceed the true value of P(d) - P(0). CPSC's assessment of the potential carcinogenic risk due to the inhalation of formaldehyde released by UFFI is based primarily upon GLOBAL 79's 95% upper confidence limits on excess risk.

In order to illustrate the idea of a 95% upper confidence limit the following simple example is given. Twenty slips of paper are placed in a hat. On 19 slips the number 1000 is written, and on 1 slip the number 0 is written. A slip of paper is selected at random so that each slip has a 5% chance of being selected. The number on the selected slip is taken to be an upper limit on Reggie Jackson's batting average in 1982. This upper limit has been generated by a 95% upper confidence limit procedure since the procedure had a 95% chance of generating a number which equalled or exceeded Reggie's batting average for 1982. Although this example is extremely simplified, it does indicate that something can be a valid 95% upper confidence limit without being a very informative indicator of the quantity it is trying to be an upper limit on. In general statisticians do strive to make their 95% upper confidence limit procedures yield limits which are as close as possible to the unknown underlying quantity they are trying to bound but still exceed it 95% of the time. However, it is important to remember that an upper limit is an upper bound and not an estimate. Upper limits do tend to indicate a range of the possibilities but not all of the possibilities within that range are equally likely to be the true value of the unknown being bounded. Normally, the values in the range that are near the best estimate are more likely to be equal to the true value of the unknown, and the values further away from the best estimate are less likely to be equal to the true value of the unknown.

The differences between GLOBAL 79's maximum likelihood estimates of excess risk and the corresponding 95% upper confidence limits on excess risk are substantial. Figures 2 and 3 illustrate these differences for doses between 0 and 1 ppm. Table 4 indicates the maximum likelihood estimates, the 95% upper confidence limits, and their ratios for several dose levels. For the dose levels discussed in terms of formaldehyde released from UFFI the 95% upper confidence limit is frequently between 100 to 1000 or more times as large as the corresponding maximum likelihood estimate.

Figure 2. The Differences Between GLOBAL 79's Maximum Likelihood Estimates of Risk (Best-Fit-of-Data Estimates) and the Corresponding 95% Upper Confidence Limits on Risk

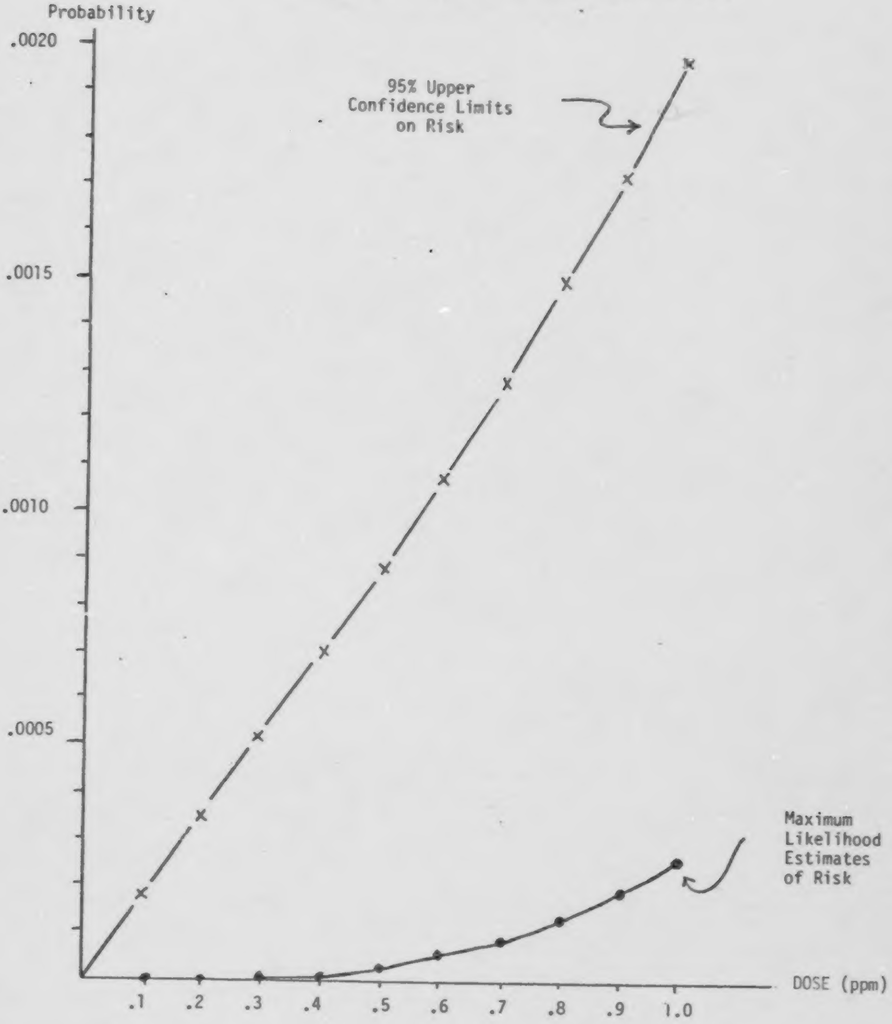


Figure 3. The Differences Between GLOBAL 79's Maximum Likelihood Estimates of Risk (Best-Fit-of-Data Estimates) and the Corresponding 95% Upper Confidence Limits on Risk (An Enlargement of Figure 2)

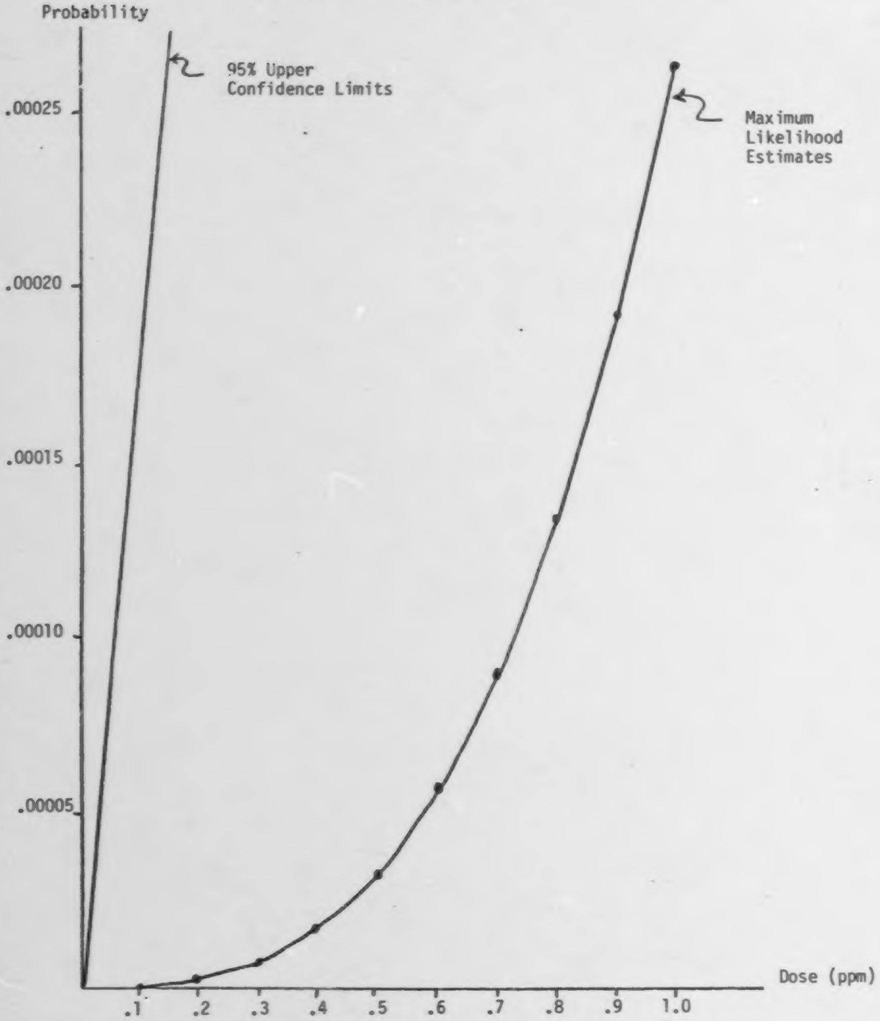


Table 4. GLOBAL 79's Maximum Likelihood Estimates of Risk, 95% Upper Confidence Limits on Risk, and Their Ratios

| Dose (ppm) | Maximum Likelihood Estimate | 95% Upper Confidence Limit | Ratio: 95% UCL / MLE |
|---|---|---|---|
| .001 | .264(-12) | .170(-5) | 6,439,393.94 |
| .01 | .264(-9) | .170(-4) | 64,393.94 |
| .02 | .211(-8) | .341(-4) | 16,161.14 |
| .03 | .713(-8) | .511(-4) | 7,166.90 |
| .04 | .169(-7) | .682(-4) | 4,035.50 |
| .05 | .330(-7) | .852(-4) | 2,581.82 |
| .06 | .570(-7) | .102(-3) | 1,789.47 |
| .07 | .905(-7) | .119(-3) | 1,314.92 |
| .08 | .135(-6) | .136(-3) | 1,007.41 |
| .09 | .192(-6) | .154(-3) | 802.08 |
| .1 | .264(-6) | .171(-3) | 647.73 |
| .2 | .211(-5) | .343(-3) | 162.56 |
| .3 | .713(-5) | .518(-3) | 72.65 |
| .4 | .169(-4) | .698(-3) | 41.30 |
| .5 | .330(-4) | .885(-3) | 26.82 |
| .6 | .570(-4) | .108(-2) | 18.95 |
| .7 | .905(-4) | .128(-2) | 14.14 |
| .8 | .135(-3) | .150(-2) | 11.11 |
| .9 | .192(-3) | .172(-2) | 8.96 |
| 1.0 | .264(-3) | .197(-2) | 7.46 |
| 2.1 | .244(-2) | .886(-2) | 3.63 |
| 5.6 | .453(-1) | .723(-1) | 1.60 |
| 14.1 | .523 | .588 | 1.12 |

## 5. Low Dose Linearity

The 95% upper confidence limits on excess risk computed by GLOBAL 79 are nearly linear in dose over the low dose region. As indicated in Figure 4, this approximate linearity exists for the formaldehyde data for doses between 0 and .5 ppm where the 95% upper confidence limit on the excess risk at dose $d$ is approximately

$$.00165\, d \quad . \tag{5.1}$$

Furthermore, the slope, .00165, of the straight line approximating the 95% upper confidence limits in the low dose region is relatively large for cancer risks (reaching 1/10,000 before .1 ppm); so that, relatively speaking, the straight line is a "rapidly rising" straight line. We have already noted in Section 4 that this behavior of the 95% upper confidence limits on excess risk in the low dose region does not coincide with the nonlinear, very slow rising behavior of the maximum likelihood estimates of excess risk in the low dose region.

Is the "rapidly rising" straight line a reasonable behavior for the 95% upper confidence limits on excess risk for situations like those indicated by the experimental data concerning formaldehyde?

### 5.1 An Argument for Some Low Dose Linearity

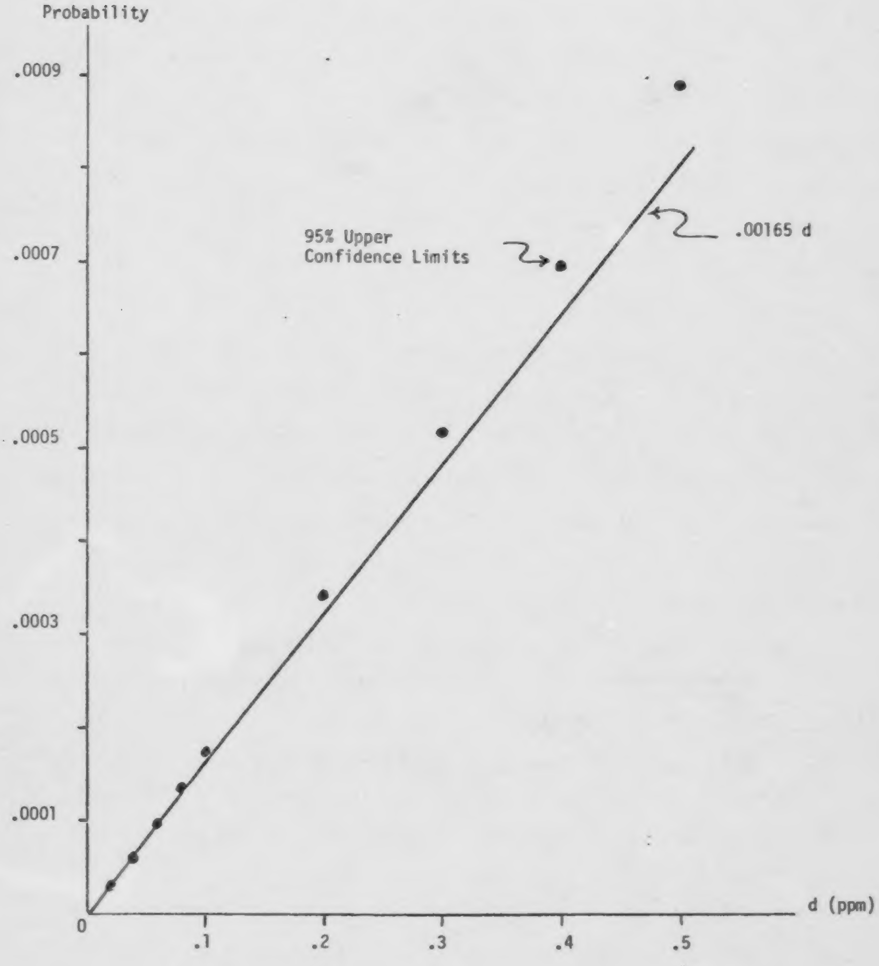
The most frequent argument for "some" low dose linearity is the notion that the effects of formaldehyde released by UFFI add on to the effects of formaldehyde normally present and possibly add on to the effects of other potential carcinogens. In this scenario $d$ ppm of formaldehyde released from UFFI corresponds to $d$ "added on" to a background dose. If $b$ is the background dose and $d$ is the amount of formaldehyde released by UFFI, then the total dose $D$ is

$$D = b + d$$

and the excess risk corresponding to $d$ is

$$P(b+d) - P(b) \ .$$

Figure 4. The Rapidly Rising Linearity of the 95% Upper Confidence Limits on Excess Risk



If P(b) is substantially nonzero, then there will most likely be "some" linear component to the excess risk P(b+d) - P(b) as depicted in Figure 5.

There are at least 3 critical points to keep in mind here. First, P(b) must be substantially positive; that is, there must be a positive background (spontaneous) response rate. Second, formaldehyde must interact with the ongoing background carcinogenesis. Third, there can be a great deal of difference between "some" linearity and a "rapidly rising" straight line; that is, the possibility of "some" linear component to the excess risk may not justify the "rapidly rising" straight line indicated by GLOBAL 79's 95% upper confidence limits on excess risk. (All straight lines are linear, but they certainly aren't all equal.)

### 5.2 The Background Response Rate

Malignant nasal cancer in rats appears to be a rare event. This historical observation is supported by the 0/160 observed response rate at 0 ppm in the CIIT study. Thus, the substantial positive background response rate P(b) called for in the above argument for low dose linearity of the 95% upper confidence limits on excess risk appears to be questionable.

There are, of course, several qualifying remarks which could be made concerning the background response rate such as,

a) the rats in the CIIT study were kept in a laboratory environment and were not subject to the everyday "real world" environmental hazards;

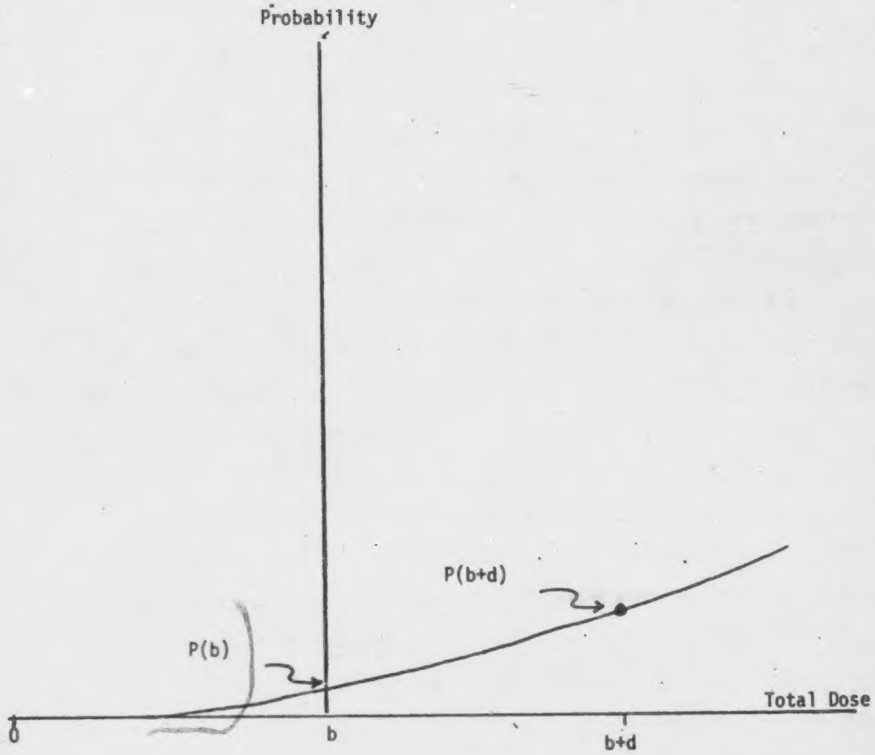
b) malignant nasal cancer can occur in humans;

c) malignant nasal cancer might not be the response produced by formaldehyde in humans;

d) there is an approximate 25% incidence of cancer in the general human population; etc.

While these qualifiers may be true, they refer to factors which were not part of the CIIT experiment; so that, the experimental outcomes do not provide

Figure 5. The Possibility of Some Low Dose Linearity When the Dose d Adds Onto the Background Dose b


Probability
P(b+d)
P(b)
Total Dose
0
b
b+d

any experimental evidence concerning the effects of these factors.

Since factors which do not influence the experimental outcomes cannot effect the outcome of a selected confidence limit procedure, the only way for these factors to be taken into account is in the subjective value judgement of which confidence limit procedure to select. GLOBAL 79 has selected an upper confidence limit procedure which produces "rapidly rising" linear 95% upper confidence limits on excess risk whenever there is any positive response observed at the highest experimental dose level. For example, Figure 6 and Table 5 indicate the 95% upper confidence limits and maximum likelihood estimates of excess risk if the CIIT experiment would have yielded 0/160, 0/160, 0/160 and 1/160 at 0, 2.1, 5.6 and 14.1 ppm respectively.

The tendency for GLOBAL 79 to produce "rapidly rising" linear 95% upper confidence limits on excess risk virtually irrespective of the experimental data is further illustrated in Figure 7. There the 95% upper confidence limits on excess risk in the low dose range are depicted for both the actual experimental outcome (0/160, 0/160, 3/160, and 87/160) at 0, 2.1, 5.6, and 14.1 ppm respectively and the hypothetical outcome (0/160, 0/160, 0/160, and 1/160) at 0, 2.1, 5.6, and 14.1 ppm respectively. The 95% upper confidence limits do differ by a factor of about 2, but that difference seems relatively small compared to the big difference in experimental outcomes. Thus, it appears that the "rapidly rising" linear behavior of the GLOBAL 79 95% upper confidence limits is more of a property of the confidence limit procedure itself and not a property of the underlying experimental data.

Figure 6. The Rapidly Rising Low Dose Linearity of the 95% Upper Confidence Limits on Excess Risk Even for the Hypothetical Experimental Outcome 0/160, 0/160, 0/160 and 1/160 at 0, 2.1, 5.6 and 14.1 ppm Respectively

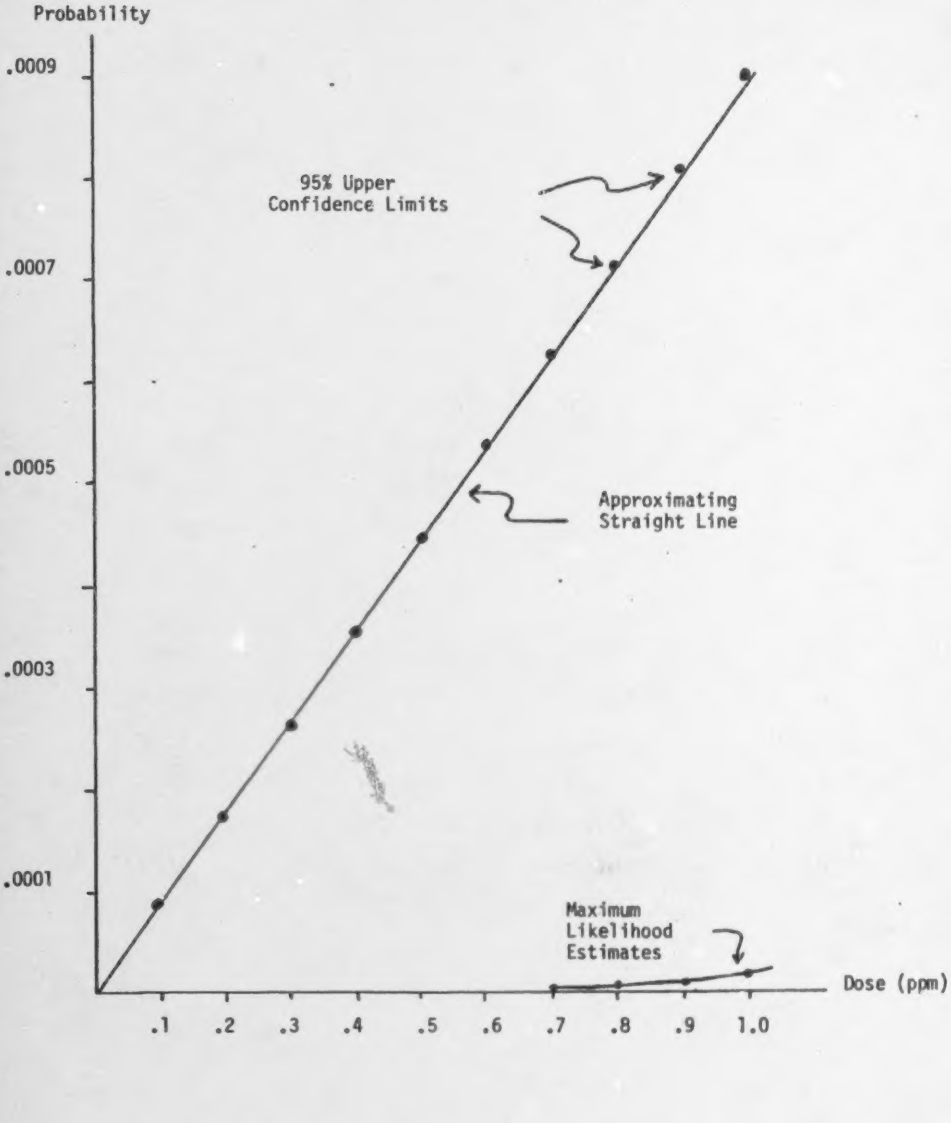
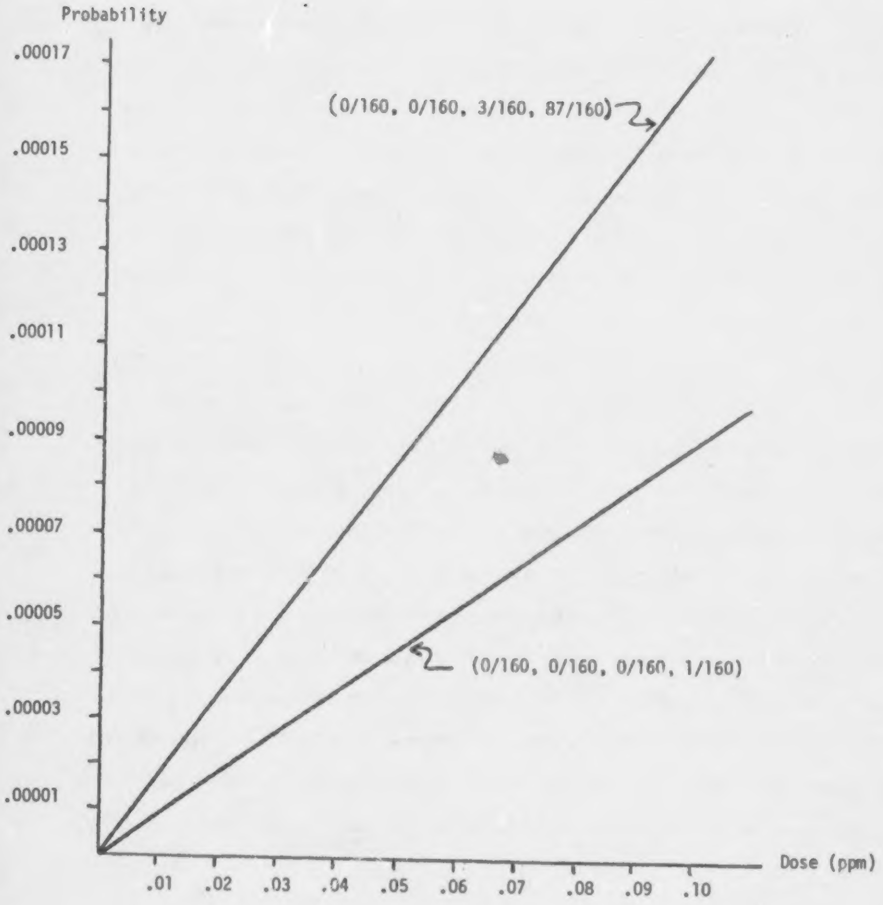


Table 5. GLOBAL 79's Maximum Likelihood Estimates of Excess Risk and 95% Upper Confidence Limits on Excess Risk for the Hypothetical Experimental Outcome 0/160, 0/160, 0/160 and 1/160 at 0, 2.1, 5.6 and 14.1 ppm Respectively

| Dose (ppm) | Maximum Likelihood Estimate | 95% Upper Confidence Limit | Ratio: $\frac{95\% \text{ UCL}}{\text{MLE}}$ |
|---|---|---|---|
| .001 | .210(-14) | .895(-6) | 426,190,476.1 |
| .01 | .210(-11) | .895(-5) | 4,261,904.8 |
| .02 | .168(-10) | .179(-4) | 1,065,476.2 |
| .03 | .566(-10) | .268(-4) | 473,498.2 |
| .04 | .134(-9) | .358(-4) | 267,164.2 |
| .05 | .262(-9) | .448(-4) | 170,992.4 |
| .06 | .453(-9) | .537(-4) | 118,543.0 |
| .07 | .720(-9) | .627(-4) | 87,083.3 |
| .08 | .107(-8) | .716(-4) | 66,915.9 |
| .09 | .153(-8) | .806(-4) | 52,679.7 |
| .1 | .210(-8) | .895(-4) | 42,619.0 |
| .2 | .168(-7) | .179(-3) | 10,654.8 |
| .3 | .566(-7) | .269(-3) | 4,752.7 |
| .4 | .134(-6) | .358(-3) | 2,671.6 |
| .5 | .262(-6) | .448(-3) | 1,709.9 |
| .6 | .453(-6) | .537(-3) | 1,185.4 |
| .7 | .720(-6) | .627(-3) | 870.8 |
| .8 | .107(-5) | .717(-3) | 670.1 |
| .9 | .153(-5) | .807(-3) | 527.5 |
| 1.0 | .210(-5) | .897(-3) | 427.1 |
| 2.1 | .194(-4) | .593(-3) | 30.6 |
| 5.6 | .368(-3) | .286(-2) | 7.8 |
| 14.1 | .586(-2) | .158(-1) | 2.7 |

Figure 7. The Similarity Between the 95% Upper Confidence Limits on Excess Risk for the Two Dissimilar Experimental Outcomes (0/160, 0/160, 3/160, 87/160) and (0/160, 0/160, 0/160, 1/160) at 0, 2.1, 5.6 and 14.1 ppm Respectively



## 5.3 Other Models Incorporating Additive Backgrounds

The idea of the formaldehyde released from UFFI interacting or adding onto the ongoing carcinogenic activity can be incorporated into cancer models other than the multistage model. The CPSC report indicates that, although the linear and one-hit models do not adequately fit the data, the probit, logit, multihit and Weibull models (as well as the multistage model) do adequately fit the data. In fact, looking at the maximum likelihood fits of these models to the CIIT data in Figure 8, one could even say that the probit, logit, multihit and Weibull models fit better since they more nearly match the observed response rate of 3/160 at 5.6 ppm. The probit, logit, multihit and Weibull models were all fit with the provision for additive backgrounds using the computer program RISK81 developed by D. Krewski and J. Kovar at Health and Welfare, Canada.

Table 6 indicates RISK81's 95% upper confidence limits on excess risk for several doses in the low dose region under each of the models with additive background (probit, logit, multihit and Weibull) as well as those given by GLOBAL 79 for the multistage model. The inescapable conclusion drawn from Table 6 is that 95% upper confidence limits do not necessarily have to be so "rapidly rising" in the low dose region as implied by GLOBAL 79 for the multistage model. Furthermore, the concept of an additive background does not necessarily force the 95% upper confidence limits to be well approximated by a "rapidly rising" straight line in the low dose region. Thus, the possibility that formaldehyde released from UFFI may interact with ongoing carcinogenic activity does not by itself justify the 95% upper confidence limits indicated by GLOBAL 79 for the multistage model.

Figure 8. Maximum Likelihood Estimates of Risk under the Multistage Model and the Probit, Logit, Multihit, and Weibull Models with Additive Backgrounds.

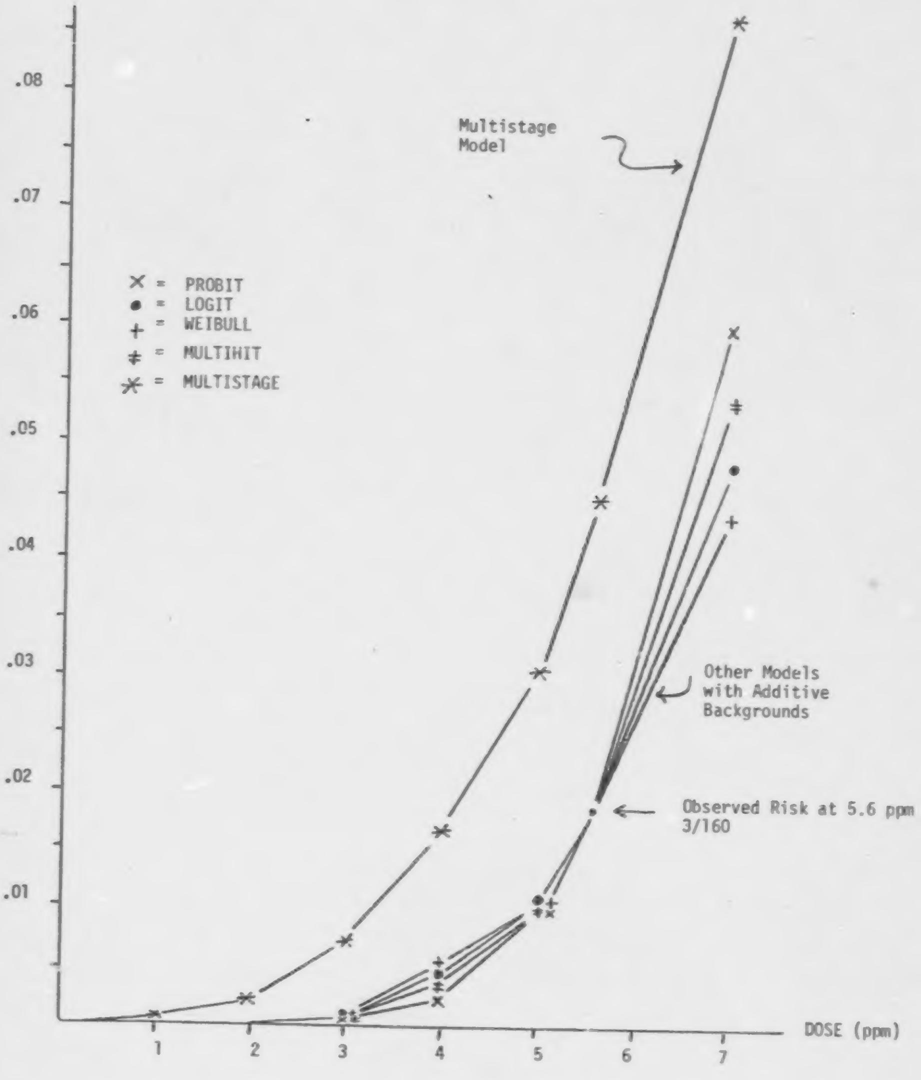


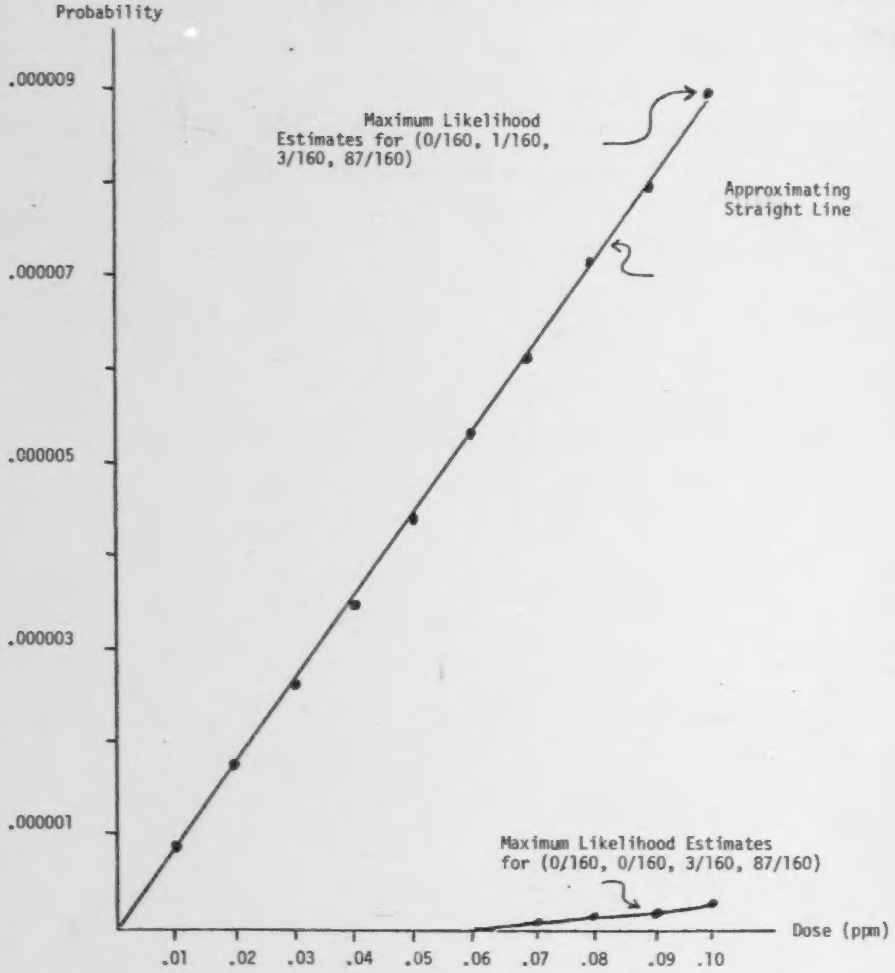
Table 6. 95% Upper Confidence Limits on Excess Risk Implied by Different Models Incorporating Additive Backgrounds and the Multistage Model

| Dose | Probit | Multihit | Logit | Weibull | Multistage |
|---|---|---|---|---|---|
| .01 | .11(-18) | .48(-17) | .37(-10) | .46(-9) | .17(-4) |
| .02 | .37(-18) | .45(-15) | .42(-9) | .38(-8) | .34(-4) |
| .03 | .96(-18) | .64(-14) | .17(-8) | .13(-7) | .51(-4) |
| .04 | .22(-17) | .42(-13) | .47(-8) | .32(-7) | .68(-4) |
| .05 | .49(-17) | .18(-12) | .10(-7) | .63(-7) | .85(-4) |
| .06 | .10(-16) | .58(-12) | .19(-7) | .11(-6) | .10(-3) |
| .07 | .21(-16) | .16(-11) | .33(-7) | .18(-6) | .12(-3) |
| .08 | .41(-16) | .38(-11) | .52(-7) | .26(-6) | .14(-3) |
| .09 | .79(-16) | .81(-11) | .79(-7) | .38(-6) | .15(-3) |
| .1 | .15(-15) | .16(-10) | .11(-6) | .52(-6) | .17(-3) |
| .5 | .25(-9) | .40(-6) | .26(-4) | .60(-4) | .89(-3) |
| 1.0 | .43(-6) | .23(-4) | .24(-3) | .41(-3) | .20(-2) |

### 5.4 Possible Low Dose Linearity of the Maximum Likelihood Estimates

The maximum likelihood estimates of excess risk can be linear themselves in the low dose region if the experimental data warrants it. For example, if instead of an observed response rate of 0/160 at 2.1 ppm in the CIIT experiment the response rate would have been even 1/160 at 2.1 ppm, then, as seen in Figure 9, the maximum likelihood estimates of excess risk would be approximatley linear in the low dose region and fairly "rapidly rising". Thus, when the experimental data suggests it, a "rapidly rising" linear picture of excess risk arises naturally in the maximum likelihood estimates without being arbitrarily forced into being by the confidence limit procedure.

Figure 9. The Low Dose Linearity of the Maximum Likelihood Estimates of Risk If There Would Have Been Observed Responses at the Lowest Positive Dose, Say 0/160, 1/160, 3/160 and 87/160 at 0, 2.1, 5.6 and 14.1 ppm Respectively



## 6. The Empirical Behavior of GLOBAL 79

On the average, how much larger are the 95% upper confidence limits on excess risk given by GLOBAL 79 than the actual excess risk? On the average, how do the maximum likelihood estimates of excess risk compare to the actual excess risk? This section gives an indication of the answers to these important questions. In particular this section will show that in the case of the CIIT experiment, unless any low dose linearity extends well beyond the "low dose region" and includes the doses all the way up to 5.6 ppm which is the second largest experimental dose, the 95% upper confidence limits on excess risk tend to grossly overstate the actual risk while the maximum likelihood estimates do not grossly understate the risk.

Let $p_d$ denote the actual probability of a malignant nasal cancer in a rat exposed to d ppm of formaldehyde for the duration of the CIIT experiment. In what follows the $p_d$'s are specified and then

(i) each "possible" experimental outcome is considered,
(ii) the likelihood of each outcome is determined,
(iii) the value of the 95% upper confidence limits on excess risk is calculated for each outcome,
(iv) the value of the maximum likelihood estimate of excess risk is calculated for each outcome,
(v) the mean over the outcomes of these 95% upper confidence limits and maximum likelihood estimates is calculated, and finally
(vi) the ratios of these means to the specified excess risks calculated.

Thus, in what follows we shall specify the underlying carcinogenic risks, and then examine the average 95% upper confidence limits and maximum likelihood estimates generated by GLOBAL 79.

In the first set of trials we shall specify that

(i) $p_0 = 0$, $p_{5.6} = 3/160$, $p_{14.1} = 87/160$;

(ii) the observed response rates are 0/160, 3/160, and 87/160 at 0, 5.6, and 14.1 ppm respectively;

(iii) $p_d$ is linear from d=0 ppm to d=2.1 ppm; that is, $p_d = (d/2.1)p_{2.1}$;

(iv) $p_{2.1}$ is a fraction, f, of what $p_{2.1}$ would be if the risk were linear over the whole range from d=0 ppm to d=5.6 ppm; that is, $p_{2.1} = f(2.1/5.6)(3/160) = .00703\ f$ ; and

allow the experimental outcomes to vary over 0/160, 1/160, 2/160, etc. at 2.1 ppm. The ratios of the mean maximum likelihood estimate of excess risk at d=1.0, .5, and .1 ppm to the specified value of $p_d$ corresponding to linearity between d=0 and d=2.1 (that is $p_d = (d/2.1)p_{2.1}$) are given in Table 7. Analogous ratios are also given in Table 7 for the mean 95% upper confidence limits on excess risk at d=1.0, .5, and .1 ppm. For example, when $p_{2.1}$ is 1/100-th of what the risk would be if the risk were linear over the entire range from d=0 ppm to d=5.6 ppm, ($p_{2.1} = f(2.1/5.6)(3/160)$ with f=.01) , then the 95% upper confidence limit on the excess risk at d=1.0 ppm would be on the average 59.3 times greater than what the risk at 1.0 ppm would be if the excess risk was linear between d=0 ppm and d=2.1 ppm. Thus, in this example, where the excess risk is specified to be linear from d=0 to d=2.1 but not linear all the way from d=0 to d=5.6, the 95% upper confidence limit on the excess risk at d=1.0 ppm averages 59.3 times too large. The observed response rate of 0/160 at 2.1 ppm in the CIIT experiment suggests that any low dose linearity would probably not even extend from d=0 to d=2.1; so that, the 59.3 probably understates the overestimation of the 95% upper confidence limit on the excess risk at d=1.0 ppm.

Table 7 also suggests that the "best-fit-of-data" or maximum likelihood estimates of excess risk generated by GLOBAL 79 do not tend to greatly understate the excess risks even when these risks are linear between d=0 ppm and d=2.1 ppm.

For example, if the excess risk at 2.1 ppm is 1/100-th of what it would be if excess risks were linear all the way from d=0 ppm to d=5.6 ppm (that is, $p_{2.1} = f(2.1/5.6)(3/160)$ with f= .01), then the average maximum likelihood estimate of the excess risk at d=.5 ppm would be 2.0 times as large as what $p_{.5}$ would be if the excess risk were linear from d=0 ppm to d=2.1 ppm. Here, when the excess risk is assumed to be linear between d=0 and d=2.1 but not linear all the way from d=0 to d=5.6, the maximum likelihood estimate on the average actually overestimates the excess risk at d=.5 ppm instead of grossly underestimating the risk. If, as the CIIT data suggests, any low dose linearity would probably not extend out to 2.1 ppm, even the degree of underestimation suggested in some places in Table 7 for the average maximum likelihood estimate of excess risk is an overstatement. Thus, Table 7 suggests that the maximum likelihood estimate of excess risk is not unreasonably small.

In the first set of trials the observed response rate at 5.6 ppm was kept fixed at 3/160 which equals that observed in the CIIT experiment. Just to make sure that this fixed response rate did not bias the conclusions, a second set of trials was performed in the same way as the first set except that the observed response rate at 5.6 ppm was allowed to vary over 0/160, 1/160, 2/160, etc. Table 8 is analogous to Table 7 but the means are over all possible outcomes with the observed response rates being allowed to vary at both 2.1 ppm and 5.6 ppm. The conclusions implied by Table 8 are the same as those implied by Table 7. Namely, it takes more than just low dose linearity to make GLOBAL 79's 95% upper confidence limits on excess risk an accurate reflection of the true underlying excess risks; it takes linearity all the way from d=0 ppm up to d=5.6 ppm which is well into the experimental dose range and such linearity is not supported by the CIIT data. In addition the maximum likelihood estimates of excess risk produced by GLOBAL 79 do not demonstrate a tendency to greatly understate the risk.

Table 7

Mean Behavior of GLOBAL 79 Maximum Likelihood Estimates of Excess Risk and 95% Upper Confidence Limits on Excess Risk

| Target | f | Ratio of Mean Maximum Likelihood Estimate of Risk at Target Dose to Presumed Risk at Target Dose * | Ratio of Mean 95% Upper Confidence Limit on Risk at Target Dose to Presumed Risk at Target Dose * |
|---|---|---|---|
| 1.0 | .001 | 78.88 | 587.7 |
| 1.0 | .01 | 7.92 | 59.3 |
| 1.0 | .05 | 1.62 | 12.3 |
| 1.0 | .1 | .84 | 6.4 |
| 1.0 | .5 | .27 | 1.7 |
| 1.0 | 1.0 | .25 | 1.1 |
| .5 | .001 | 19.74 | 528.9 |
| .5 | .01 | 2.0 | 53.4 |
| .5 | .05 | .43 | 11.1 |
| .5 | .1 | .25 | 5.8 |
| .5 | .5 | .15 | 1.6 |
| .5 | 1.0 | .19 | 1.1 |
| .1 | .001 | .82 | 510.1 |
| .1 | .01 | .11 | 51.5 |
| .1 | .05 | .06 | 10.7 |
| .1 | .1 | .06 | 5.6 |
| .1 | .5 | .12 | 1.6 |
| .1 | 1.0 | .18 | 1.1 |

* Presumed Risk at Target Dose = the risk at the target dose if the risk at the target dose were linearly related to the risks at 0 ppm and 2.1 ppm.

Table 8

Mean Behavior of GLOBAL 79 Maximum Likelihood Estimates of Excess Risk and 95% Upper Confidence Limits on Excess Risk With the Observed Rates Varying at Both 2.1 ppm and 5.6 ppm

| Target Dose | f | Ratio of Mean Maximum Likelihood Estimate of Risk at Target Dose to Presumed Risk at Target Dose * | Ratio of Mean 95% Upper Confidence Limit on Risk at Target Dose to Presumed Risk at Target Dose * |
|---|---|---|---|
| 1.0 | .001 | 78.90 | 606.0 |
| 1.0 | .01 | 7.94 | 61.1 |
| 1.0 | .1 | .86 | 6.6 |
| 1.0 | .25 | .40 | 3.0 |
| 1.0 | .5 | .27 | 1.8 |
| 1.0 | 1.0 | .22 | 1.2 |
| .07 | .001 | .45 | 528.2 |
| .07 | .01 | .10 | 53.3 |
| .07 | .1 | .08 | 5.8 |
| .07 | .25 | .09 | 2.6 |
| .07 | .5 | .11 | 1.6 |
| .07 | 1.0 | .14 | 1.1 |

* Presumed Risk at Target Dose = the risk at the target dose if the risk at the target dose were linearly related to the risks at 0 ppm and 2.1 ppm.

## 7. Conclusions

Although there are several aspects to human cancer risk assessment, this paper has focused on only low dose risk extrapolation using the multistage model and the methodology implemented in the computer program GLOBAL 79. The paper is not a universal condemnation of the multistage model or GLOBAL 79 but rather a perspective on its use in situations like the CIIT formaldehyde experiment where there is no direct experimental evidence of increased risk at the lower positive experimental dose or doses.

We have seen that GLOBAL 79 was limited in its ability to reflect the nonlinearity or flatness of the dose response relationship in the lower portion of the experimental dose range (from 0 ppm to 5.6 ppm). The "best-fit-of-data" or maximum likelihood estimates determined by GLOBAL 79 for the low dose region were essentially forced to be greater than the data itself warranted due to the limitation imposed by the number of dose levels in the CIIT experiment.

The substantial difference between GLOBAL 79's maximum likelihood estimates of excess risk and the 95% upper confidence limits on excess risks have been documented. These differences appear to often be large enough to substantially alter a regulatory risk assessment. Analogous differences would also occur if the level of confidence was changed from 95% to either 90% or 99%. Therefore, the reason for the large difference between the best estimate and the upper confidence limit is not the level of the confidence limit but rather the chosen confidence limit procedure itself.

The particular confidence limit procedure implemented in GLOBAL 79 is designed to essentially always yield "rapidly rising" confidence limits which are nearly linear for low doses. This rapidly rising linearity is not a property of all confidence limit procedures. Rather it is a property that is built into the specific confidence limit procedure used in GLOBAL 79.

We have examined several intended justifications for the characteristics of the GLOBAL 79 confidence limit procedure. The justification for "some" linearity due to the possibility of additive backgrounds and the potential interaction of formaldehyde with other ongoing carcinogenic processes has some theoretical merit but doesn't necessarily support the kind of "rapidly rising" linearity produced by GLOBAL 79. Furthermore, the other low dose extrapolations models which are sited by CPSC as adequately fitting the CIIT data and which incorporate additive backgrounds do not produce upper confidence limits with the "rapidly rising linearity" produced by GLOBAL 79. Most of the other intended justifications are based upon assumptions or speculations which are not part of the CIIT experimental evidence.

Examples are given which show that the 95% upper confidence limits produced by GLOBAL 79 are not very sensitive to the experimental outcomes in the sense that two dissimilar outcomes from the same experiment can yield remarkably similar upper confidence limits on excess risk.

The empirical behavior of GLOBAL 79 was observed in a completely specified situation analogous to the CIIT experiment. On the average the 95% upper confidence limits on excess risk could easily grossly overstate the excess risk. On the other hand the best-fit-of-data estimates (maximum likelihood estimates) do not grossly understate the excess risk. Hence, the tendency to overemphasize the 95% upper confidence limits and dismiss the best-fit-of-data estimates as being essentially irrelevent seems at best highly questionable.

The low dose cancer risk extrapolation for items like formaldehyde where there is no direct experimental evidence of risk at low doses requires a thorough understanding of the properties of the statistical procedures employed. Some perspectives on the use of the multistage model as implemented in GLOBAL 79 have been given. In particular, the worth of the 95% upper confidence limits on excess risk in these situations has been challenged.

## REFERENCES

Crump, K. S. (1981). An improved procedure for low-dose carcinogenic risk assessment from animal data. Journal of Environmental Pathology and Toxicology. (To Appear)

# Statistical Methodology
# for Toxicological Research

## MRS. T

## Documentation

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# Statistical Methodology for Toxicological Research

## 1. Historical Background

The Institute of Statistics, Texas A&M University, became interested in developing a new statistical methodology for carcinogenic risk assessment in 1974. Our initial research was supported by a contract with the Food and Drug Administration (FDA) and a subsequent contract with the National Center for Toxicological Research (NCTR). Dr. H.O. Hartley spearheaded the initial research team which also included Drs. C.E. Gates, J.H. Matis, R.L. Sielken Jr. and H.D. Tolley as well as several graduate students.

The initial contract research was summarized in Hartley and Sielken [1977a,b]. In addition a comprehensive computer implementation of our initial Statistical Methodology for Toxicological Research was prepared by R.L. Sielken Jr. A simple rearrangement of the letters SMTR has led to the computer program being called "MRS. T". The program was made available to government agencies, industry, and the academic community at cost. MRS. T was designed to be used as both a powerful research tool and a statistical analyzer of experimental data from toxicological studies. MRS. T provided a statistical analysis of real experimental data. In addition the program had the capability of simulating experimental data. This capability was particularly useful in evaluating the effectiveness of the risk estimation procedures and also alternative experimental designs.

Pharmacokinetic principles leading to the "general product" model were investigated during 1977-1979. The first of eventually two general biological foundations for our general product model was indicated in Dr. Sielken's presentation "Stochastic Models for Carcinogenic Processes and Risk Assessment" at the 1979 spring meetings of the Biometrics Society in New Orleans. These foundations were further clarified in talks by Dr. Hartley at the 35-th Annual Conference on Applied Statistics in Princeton in December, 1979, and at the International Symposium on Statistics and Related Topics in Ottawa in May, 1980. The foundations are documented in Hartley, Tolley, and Sielken [1980].

Since 1980 Dr. Sielken has served as a private consultant to the Society of Toxicologists' committee reviewing NCTR's $ED_{01}$ study. That committee's report was presented at the national Society of Toxicologists meeting in San Diego on March 5, 1981, and is to be published in the first issue of the Society of Toxicologists' new journal Fundamental and Applied Toxicology in 1981. The portion of that report entitled "Risk Assessment Using Time" contains many new developments in carcinogenic risk assessment and was presented at the spring meetings of the Biometric Society in Richmond on March 24, 1981. That material contains new generalizations of the Hartley-Sielken model and demonstrations of their application as well as suggestions for new risk characterizations which realistically include time.

2. A New MRS. T

The support of the Society of Toxicologists, the American Industrial Health Council, the National Institute of Health, and Texas A&M University has made possible the development of a new MRS. T. The new computer implementation MRS. T 1981 incorporates many new developments in carcinogenic risk assessment and supersedes the previous MRS. T.

Since cancer research continues, MRS. T 1981 will no doubt have successors and companions. Anyone acquiring a version of MRS. T from Dr. Sielken will of course be notified of these successors and companions as they become available.

MRS. T 1981, like her forerunner, is designed to not only provide a statistical analysis of real experimental data but also has the capability of simulating experimental data for research purposes.

## 3. Organization of the Documentation for MRS. T 1981

Section 4 provides a self-contained background for risk assessment using time including

a.) an introduction to time-to-response experiments,

b.) the historical role of time in risk assessment,

c.) basic risk models incorporating time of exposure,

d.) alternative interpretations of a "response",

e.) biological foundations for risk models,

f.) parameterizations and generalizations of the basic risk models,

f.) estimation of the parameters in the risk model,

h.) alternative experimental protocols and alternative interpretations of the "dose level",

i.) the introduction of time into the way carcinogenic risk is characterized or defined, and

j.) the estimation of carcinogenic risk.

Section 5 looks at the specific computer implementation MRS. T 1981 and her capabilities. Included in this section are discussions concerning

a.) acceptable formats for real experimental data,

b.) descriptive information generated by MRS. T 1981 concerning the experimental data,

c.) the forms of the Hartley - Sielken model which can be fit to the data using MRS. T 1981,

d.) the procedures for estimating the model parameters,

e.) information on the goodness-of-fit of the estimated model to the experimental data, f.) risk characterizations provided by MRS. T 1981, and

g.) simulation capabilities.

Section 6 indicates the specific input instructions for using MRS. T 1981.

Appendix A contains a short summary of the input instructions.

Appendix B illustrates the input and output for MRS. T 1981. Included in Appendix B are small examples illustrating both ways of describing experimental data as well as a simulation example.

Appendix C describes the computation of initial estimates of the risk model parameters.

Appendix D describes the dimensions of the storage arrays in the computer program.

## 4. Risk Assessment Using Time

### 4.1 Introduction to Time-to-Response Experiments

A properly conducted, long-term chronic toxicity test is the most definitive procedure for obtaining direct evidence on chemically induced tumors in the mammalian species.

The $ED_{01}$ study undertaken by the National Center for Toxicological Research (NCTR) is certainly one of the largest and best designed examples of a chronic toxicity test. With 24,192 BALB/c female mice allocated to 81 different treatment groups and fed 2-acetylaminofluorene (2-AAF), the $ED_{01}$ study provided an unusually large set of raw data which can be analyzed by the new improved cancer risk assessment procedures. Some of the particularly important characteristics of the $ED_{01}$ experiment are

(a) several dose levels including the zero dose level and both relatively low and relatively high dose levels,

(b) essentially six replicates of the experiment corresponding to the six Specific Pathogen Free - Defined Flora "barrier" rooms, and

(c) serial sacrifices beginning at 9 months and ending at 33 months effectively covering the animal's lifetime.

The availability of extensive time-to-response information due to the serial sacrifices and other causes of death is an extremely important aspect of the experiment.

The tremendous effort associated with the data gathering in such a study should be accompanied by commensurate efforts in risk assessment modeling and risk characterization.

MRS. T 1981 utilizes a general risk assessment model which includes both dose level and time of exposure. This general model has been shown to fit the $ED_{01}$ data quite well (Re-Examination of the $ED_{01}$ Study - Risk Assessment Using Time, 1981). Furthermore, when the model was applied to each of the six rooms, there was a considerable room-to-room consistency in the individual risk assessments. This consistency is, of course, very important for many reasons including the fact that most private experiments are more nearly the size of one room than the entire $ED_{01}$ study. In addition, several new ways of characterizing the risk at a particular dose level have been developed. These characterizations give rise to some new definitions of an "acceptable risk" which realistically include time.

## 4.2 The Historical Role of Time in Risk Assessment

Before the $ED_{01}$ study almost all of the experimental toxicity data was quantal response data. Such response-rate data (as opposed to time-to-response data) focused on the percentage of animals exhibiting a carcinogenic response by a single pre-set time - usually the end of experiment. The probit, logit, one-hit, gamma multihit, extreme value (Weibull), and multistage models are the dominant dose response models for quantal response toxicity data. Several excellent papers on these models have appeared (see, for instance, the review by the Scientific Committee of the Food Safety Council (1980) and the review by Krewski and Van Ryzin (1980)); so that no further review of these models is necessary here.

Of course, time has always been involved in toxicity experiments. Even in quantal response studies the experimenter usually has to decide on a maximum length of exposure and sometimes the youngest age at which to begin exposure. Furthermore, if the experimenter wants the risk associated with a fixed exposure, say a year, what is he to do with an animal that dies after half a year? If the dead animal has no response before its death halfway through its intended exposure, would it have developed a response in the remaining exposure if it had lived? These and similar decisions and questions have generally been resolved in a reasonable but definitely ad hoc fashion.

Since time is a factor in toxicity, time should be meaningfully included in risk assessment. It makes a difference whether it takes 30 days or 30 years of exposure to a carcinogen to significantly increase the risk of developing a tumor. Yet this element of time is essentially missing from the current definition of carcinogenic risk. Currently, a dose level which increases the lifetime risk by .000001% might be considered "virtually safe." However, if at this dose level the increased risk required only a brief exposure and led to a rapid appearance of tumors, then the loss of useful years might easily be interpreted as too great. Alternatively, if the increased appearnace of tumors only occurred very late in life after many years of exposure, then the benefits of the chemical might be given greater consideration. The need has always been there to consider time as an important dimension of the problem and not as a nuisance parameter.

## 4.3 Risk Models Incorporating Time of Exposure

One of the earliest and most widely considered models for carcinogenic risk as a function of both dose level and time of exposure was developed by Hartley and Sielken (1977) for NCTR. In the simplest Hartley-Sielken model the probability of developing a carcinogenic response by time T when exposed to a dose level, d, under a particular experimental protocol is represented by

$$P(T,d) = 1 - e^{-g(d)H(T)} \qquad (4.3.1)$$

where g is a function of dose but not time and H is a function of time. The interpretation of the model P(T,d) is that in a large population of test animals a fraction, 1 - P(T,d), could be exposed to a dose level d and be response free after T units of time. The model P(T,d) includes both the animal-to-animal variability in the population as well as the randomness in the behavior of the carcinogen.

The time to "response" can be interpreted very generally as the time to any particular "response" of interest. For example, a "response" could be

(1) bladder carcinoma of a particular severity (say grade $\geq$ 2),
(2) bladder hyperplasia and/or carcinoma,
(3) a carcinoma in either the liver or bladder,
(4) a carcinoma anywhere,
(5) any tissue or organ failure,
(5) a "debilitating" tumor,
(7) a particular type of tumor develops to the point where it begins to metastisize,
(8) the second tumor, or
(9) death due to cancer.

Thus, the occurrence of a response might or might not require a specified severity and might or might not refer to a particular site or group of sites. The time to response could be the time until any specified event of interest.

Of course, the particular values for g(d) and H(T) in (4.3.1) depend upon the particular meaning of "response" being used.

## 4.4 Biological Foundations for Risk Models

In Hartley, Tolley, and Sielken (1980) two biological foundations for the Hartley-Sielken model are presented. Both foundations apply to a large number of more specific "deep" biological models as special cases by interpreting the "generic" concepts in terms of the specific biological mechanism applicable to a particular experimental protocol. The first foundation reflects a dynamic or compartment-analytic background in which each "compartment" involves a large number of "cells". Certain restrictions are imposed on the deterministic "transfer" of the "carcinogen" from "compartment" to "compartment" and on the stochastic transformation of a normal cell to a cancerous cell. In the second foundation the administration of the "carcinogen" leads to a "series" of "attacks" on "target areas" and the "time frequency" of these "attacks" can be related to the experimental protocol. The second foundation is described in more detail below.

It is assumed that the "target tissue" is composed of an essentially infinite number of cells. It is further assumed that the administration of the carcinogen consists of discrete "packages" which may "attack" precisely one of the cells. A cell, if attacked by a "package", will have a probability $p(d) = 1 - q(d)$ to reach the cancer "initiation stage" and a probability $q(d)$ to "repair" any damage caused by the attack before there is a chance that it will suffer a second attack. (If the probability than an individual cell undergoes more than one attack is essentially zero, then the concept of a "repair" is not necessary, and $q(d)$ is simply the probability of not reaching the cancer "initiation stage".) The basic probabilities p(d) and q(d) may depend on the "dose" d, which may reflect the "concentration" of the carcinogen in the package. All the damage to the cell required to cause initiation is done at time t of the "attack". However, the initiation stage is not reached until the $t + \tau$ where $\tau$ is a constant time. This probability model for a single cell breakdown may, for example, consist of a single stage multi-hit process or may involve several stages. As soon as at least one cell reaches the initiation stage, a response is initiated in the tissue with a response apparent at time $T = t + \tau + \eta$ where $\eta$ is a constant time. Note that neither $\tau$ nor $\eta$ depends on the dose d. However, they may be made to depend on "age" t.

The experimental protocol generates a "frequency of attacks" $h^*(t,d) = s(d)\, h(t)$ where s(d) is a function of dose but not time and h(t) denotes the standardized number of attacks between t and $t + dt$. The h(t) may also depend on age dependent changes in the physiology of the animal. If the frequency of attacks is independent of the dose, then $s(d) = 1$.

If we assume that the initiation process is completely independent from cell to cell, then the probability of the tissue to be response free at time T is given by

$$Q(T,d) = q(d)^{s(d)[H(T-\tau-\eta) - \gamma(d)]}$$

where

$$H(t) = \int_0^t h(u)du$$

and

$$\gamma(d) = \int_0^{\omega(d)} h(u)du$$

where $0 \leq t \leq \omega(d)$ is a possibly dose independent initial screening period. Introducing

$$g(d) = -\log[q(d)^{s(d)}]$$

we can write $Q(T,d)$ above in the form

$$Q(T,d) = \exp\{-g(d)]H(T-\tau-\eta)-\gamma(d)]\}$$

or simply

$$P(T,d) = 1 - e^{-g(d)[H(T)-\gamma(d)]} . \qquad (4.4.1)$$

Of course, if there are no initial screen effects, then $\gamma(d) = 0$ and (4.4.1) is identical to (4.3.1)

The Hartley-Sielken model can also be considered as a generalization of the multistage model

$$P(d) = 1 - e^{-[q_o+q_1d+q_2d^2+\ldots]}$$

which has been widely used in quantal response studies. Another generalization of the multistage model to include time to response has been proposed by Daffer, Crump, and Masterman (1980). Their general model is also of the product form

$$P(T,d) = 1 - e^{-q(d)\lambda(T)}$$

but treats $\lambda(T)$ in a nonparametric form.

## 4.5 Parameterization and Generalizations of the Risk Model

In the Hartley-Sielken model (4.3.1) the unknown functions g(d) and H(T) have usually been assumed to be nondecreasing in d and T respectively and considered in the parametric forms

$$
\begin{aligned}
g(d) &= g(d;\underline{\alpha}) = \alpha_0+\alpha_1 d+\alpha_2 d^2+\ldots+\alpha_a d^a \\
H(T) &= H(T;\underline{\beta}) = \beta_1 T+\beta_2 T^2+\ldots\beta_b T^b
\end{aligned}
\qquad (4.5.1)
$$

where $\alpha_0, \alpha_1, \ldots, \alpha_a, \beta_1, \beta_2, \ldots, \beta_b$ are nonnegative parameters and without loss of generality the β's are scaled to that $\sum_{r=1}^{b} \beta_r = 1$. These parametric forms can be generalized if necessary to

$$
\begin{aligned}
g(d) &= \sum_{s=0}^{a} \alpha_s \psi_s(d) \\
H(T) &= \sum_{r=1}^{b} \beta_r \theta_r(T)
\end{aligned}
\qquad (4.5.2)
$$

where $\psi_0(d) = 1$ and $\psi_1(d), \ldots, \psi_a(d)$ are any nonnegative functions of d while $\theta_1(T), \ldots, \theta_b(T)$ are any nonnegative, nondecreasing functions of T. For example,

$$
H(T) = \beta_1 \ln(T+1) + \beta_2 T + \beta_4 T^3 + \beta_5(e^T-1) \qquad (4.5.3)
$$

is possible.

The model (4.4.1),

$$
P(T,d) = 1 - e^{-g(d)[H(T) - \gamma(d)]} ,
$$

allows for an initial dose dependent screening period. Alternatively, there could be a dose dependent reduction in the effective exposure time. In this latter case the Hartley-Sielken model can be considered in the form

$$P(T,d) = 1 - e^{-g(d)H[T - \phi(d)]} . \qquad (4.3.4)$$

If there were D dose levels in the experiment, the $\gamma(d)$ or $\phi(d)$ would usually be treated nonparametrically as $\gamma_1, \gamma_2, \ldots, \gamma_D$ or $\phi_1, \phi_2, \ldots, \phi_D$ respectively. Theoretically, $\gamma(d)$ and $\phi(d)$ could also be considered in a parametric form analogous to $g(d)$.

Although not specifically considered in MRS. T 1981, the Hartley-Sielken model can be generalized still further to the non-product form

$$P(T,d) = 1 - e^{-\sum_{s=0}^{a} \sum_{r=1}^{b} \kappa_{sr}\, d^s [T-\phi(d)]^r}$$

or

$$P(T,d) = 1 - e^{-\sum_{s=0}^{a} \sum_{r=1}^{b} \kappa_{sr} \psi_s(d) \theta_r [T-\phi(d)]}$$

where the general functions $\psi_s$, $\theta_r$, and $\phi$ are as above. These non-product forms are to be implemented in MR. T which is planned as a companion program to MRS. T 1981.

## 4.6 Estimation of the Parameters in the Risk Model

The parameters in the Hartley-Sielken models are the $\alpha$'s, $\beta$'s, and $\gamma$'s or $\phi$'s. These parameters are restricted so that $P(T,d)$ is a cumulative distribution function in T for every d; that is, for every $d \geq 0$, $P(0,d) = 0$, $0 \leq P(T,d) \leq 1$, and $P(T_1,d) \leq P(T_2,d)$ if $T_1 < T_2$. The restricted maximum likelihood estimates of these parameters can be obtained as follows: Let there be J animals in the experiment. Then the likelihood for the experiment is

$$L = \prod_{j=1}^{J} \ell_j \ . \tag{4.6.1}$$

Let

$$p(T,d) = \frac{d\ P(T,d)}{dT}$$

be the tolerance function associated with P. Then, if the j-th animal is exposed to dose level $d_j$ and observed at time $T_j$, the j-th animal's contribution to the experiment's likelihood L is either

| | |
|---|---|
| (a) $\ell_j = 1 - P(T_j,d_j)$ | if no response has occurred by time $T_j$; |
| (b) $\ell_j = P(T_j,d_j)$ | if a response has occurred by time $T_j$ but the specific time of occurrence, say $t_j$, is only known to be $\leq T_j$; or |
| (c) $\ell_j = p(t_j,d_j)$ | if a response has occurred by time $T_j$ and the specific time of occurrence, $t_j \leq T_j$, is known. |

The parameter values which maximize L (subject to the restriction that P(T,d) be a cumulative distribution function in T) are the maximum likelihood estimates of the parameters.

It should be noted that in the maximum likelihood estimation the $T_j$'s can be sacrifice times, times of accidental death, etc. The experimenter does not have to determine "cause" of death. Furthermore, in the somewhat unusual case where some "exact" times to response ($t_j$'s) are observed this information can be fully utilized.

## 4.7 The Experimental Protocol

In the Hartley-Sielken model (4.3.1), (4.4.1), or (4.5.4) the H(T) represents the cumulative effect of the passage of T units of time. In many experimental protocols the animal is "continuously" exposed to a constant dose level d for these T units of time. However, this needn't necessarily be the case. In fact, the term "dose level, d," may be interpreted very generally. The experimental protocol might, for example, call for (i) intermittent dosing at level d, (ii) progressive or regressive dosing starting at level d, (iii) dosing starting at a fixed level and incremented by a factor of d each time a fixed amount of time elapses, and (iv) intermittent dosing at a fixed level spaced d units of time apart.

The estimated model for P(T,d) refers to the carcinogenic risk under the specific experimental protocol considered. Presumably, the effects of the passage of T units of time vary with the experimental protocol (exposure pattern); so that, each experimental protocol has its own g(d), H(T), etc.

The $ED_{01}$ study, for example, does include some data on the eventual removal of 2-AAF from the diet. This makes possible at least an initial study on the progression and regression effects of 2-AAF. It is hoped that the availability of such data will stimulate research and consideration of temporary and intermittent exposures.

## 4.8 Introducing Time into the Definition of Risk

In the quantal response studies the definition of an acceptable risk is relatively straightforward. If $\pi$ is to be the allowable increment in the spontaneous response rate, then the "virtually safe dose", d*, is defined by

$$\pi = P(d^*) - P(0).$$

Alternatively, if $\omega$ is to be allowable proportionate reduction in the spontaneous response free rate, then the virtually safe dose, d*, is defined by

$$\omega = \frac{1 - P(d^*)}{1 - P(0)} \quad .$$

In these definitions $\pi$ would be near 0 and $\omega$ near 1.

The carcinogenic risk corresponding to a particular dose level d, varies with the exposure T. (The general term "exposure" should be interpreted as the passage of time under an experimental protocol.) Although often overlooked, the above definitions of a virtually safe dose actually refer to some point in time, say T*, and have the form

$$\pi = P(T^*,d^*) - P(T^*,0) \tag{4.8.1}$$

and

$$\omega = \frac{1 - P(T^*,d^*)}{1 - P(T^*,0)} \quad .$$

This realization forces the incorporation of time into risk assessment.

Two proposals for a new definition of an acceptable risk will be made here - the "late risk dose" and the "mean free dose". Other suggestions will no doubt arise as research continues and experimental evidence accrues.

The way in which risk increases with exposure time is of paramount concern. It is certainly desirable to have any increased carcinogenic risk be predominantly associated with long-term exposures. Consider for instances Figure 1. There the risk corresponding to an exposure $T^*$ is the same for both curves A and B. Yet in curve B there is a rapid rise in risk even for short exposures. Whereas in curve A the risk increase primarily only after long exposures. Generally the "later" the risk occurs, the better.

Essentially, the "late risk dose" is the dose level corresponding to an acceptably late increase in risk. Here "late" means only after a relatively long period of exposure. Formally, if $T^{**}$ denotes a reference length of exposure and f is a fraction near 1.0, then the late risk dose, $d^{**}$, is defined by

$$P(T^{**},0) = P(f \cdot T^{**},d^{**}) \quad . \tag{4.8.2}$$

This definition is illustrated in Figures 2 and 3. Roughly speaking, it takes almost as long an exposure to $d^{**}$ to reach a risk level as it takes at the zero dose level.

Since $T^{**} - fT^{**} = (1-f)T^{**}$, the late risk dose $d^{**}$ reaches the risk level $P(T^{**},0)$ proportionately earlier than $d = 0$. Clearly, the absolute amount of earliness decreases as $T^{**}$ decreases. This seems appropriate since 3 months early out of 6 months would not usually be comparable to 3 months early out of 30 months.

In terms of the Hartley-Sielken model (4.3.1) definition (4.8.2) is equivalent to

$$g(d^{**}) = g(0)[H(T^{**})/H(fT^{**})] \quad . \tag{4.8.3}$$

Since $H(T)$ decreases as $T$ decreases, the late risk dose $d^{**}$ decreases as $f$ increases. If $H(T) = T^i$, then (4.8.3) becomes

$$\begin{aligned} g(d^{**}) &= g(0)[(T^*)^i/(fT^*)^i] \\ &= g(0)/f^i \quad , \end{aligned} \tag{4.8.4}$$

and $d^{**}$ does not depend on $T^{**}$ - a nice feature. If $H(T)$ is not simply a power of $T$ but a general polynomial, then $d^{**}$ tends to decrease as $T^{**}$ decreases. From (4.8.4) it is clear that, as $i$ increases and $H(T)$ becomes more nonlinear, $d^{**}$ increases.

The expected time to response (mean time to response)

$$E[t|d] = \int_0^{\infty} t \cdot \left[\frac{dP(T,d)}{dT}\right]_{T=t} dt$$

would probably not be a good criterion for evaluating a dose level $d$. This follows since $E[t|d]$ is greatly influenced by the value of $P(T,d)$ for very large values of $T$ and it is precisely these values of $T$ for which $P(T,d)$ is most difficult to estimate. A reasonable alternative criterion might be the mean response free period in the first $T^{***}$ months of exposure. This expected number of months without a response in the first $T^{***}$ months of exposure is

$$\text{FREE}(T^{***},d) \equiv T^{***} - \int_{0}^{T^{***}} (T^{***}-t) \cdot \left[\frac{dP(T,d)}{dT}\right]_{T=t} dt \qquad (4.8.5)$$

at dose level d. The value of T*** might be close to a "lifetime". Since FREE(T***,d) would usually decrease as d increased, the maximum d satisfying

$$\frac{\text{FREE}(T^{***},d)}{\text{FREE}(T^{***},0)} \geq 1 - \varepsilon \qquad (4.8.6)$$

where $\varepsilon$ is a small number of $0 < \varepsilon < 1$ might be called the "mean free dose". The mean free dose therefore corresponds to a 100$\varepsilon$% reduction in the response free period. The definition of the mean free dose is illustrated in Figure 4.

Figure 1. Two Examples of How Risk Might Change as the Exposure Time Changes

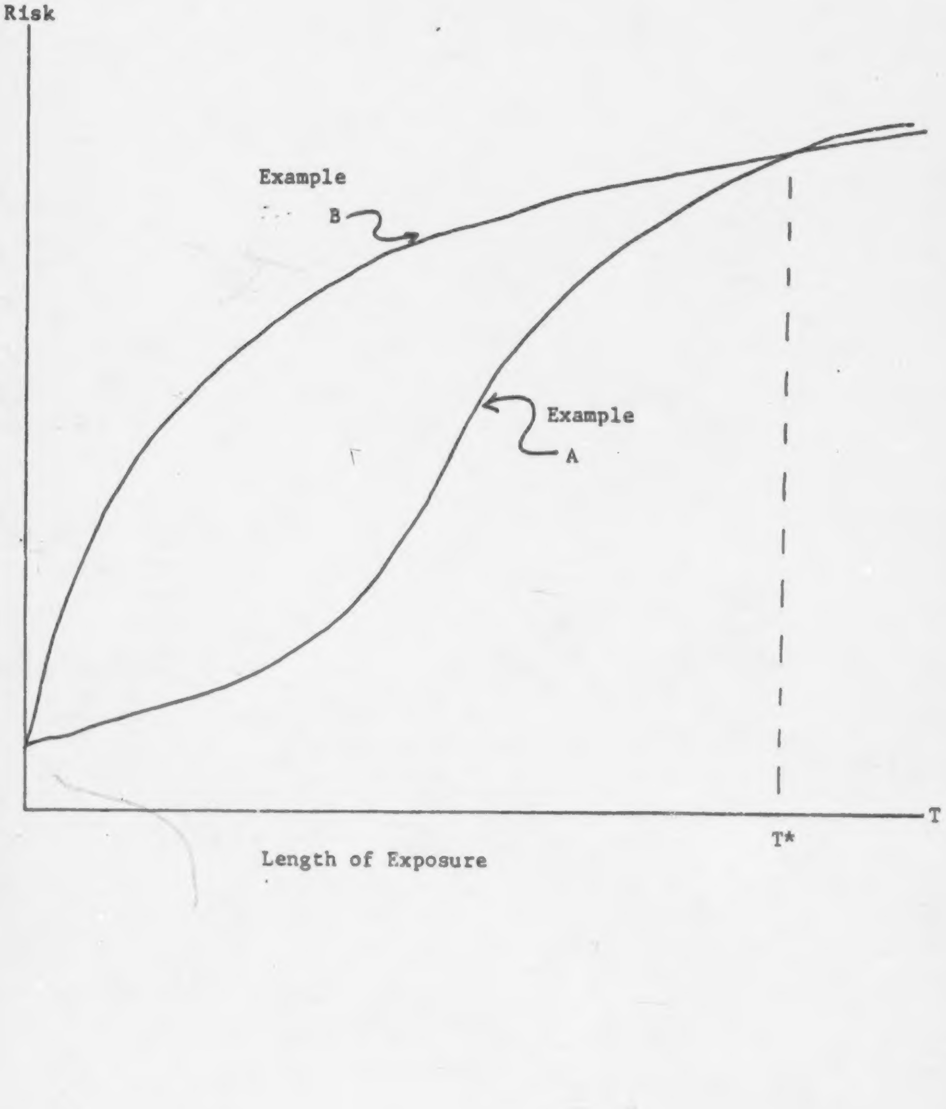


Figure 2 The Time for Nonzero Doses to Reach the Spontaneous Risk at T**

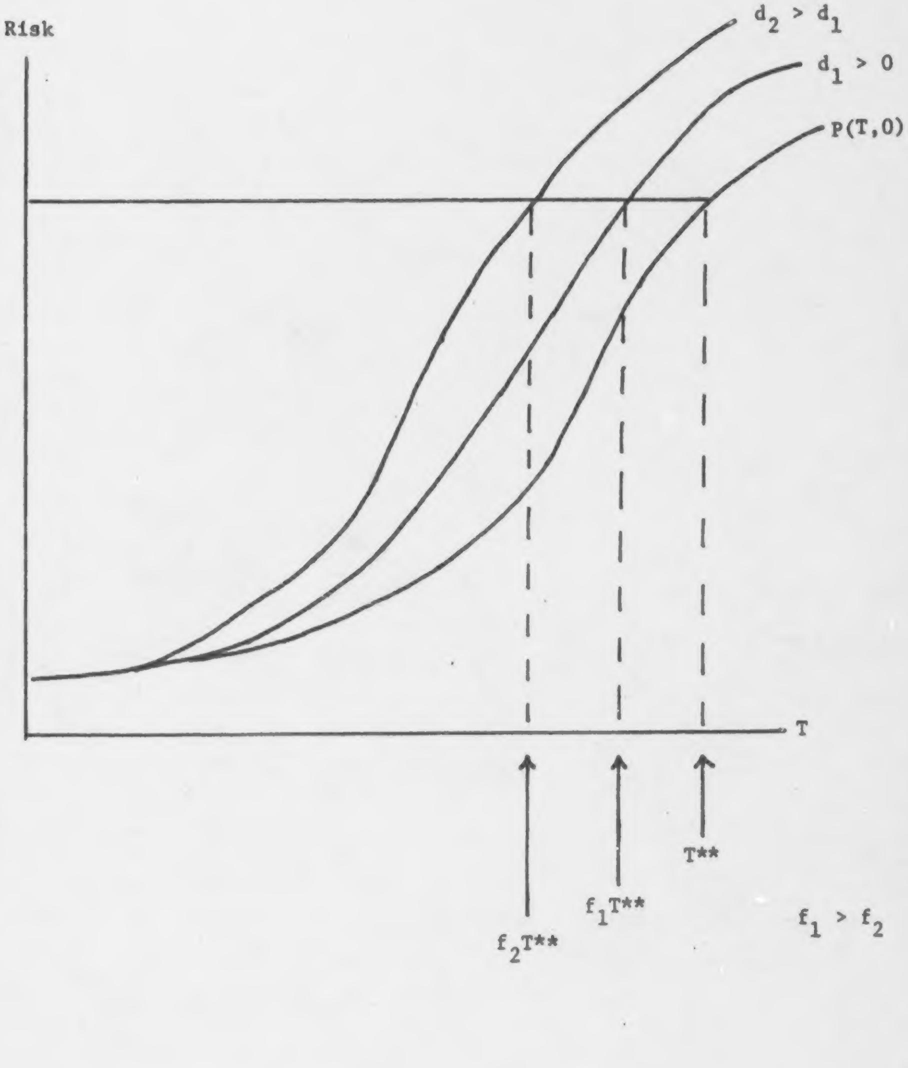


Figure 3. An Illustration of the Late Risk Dose, d**

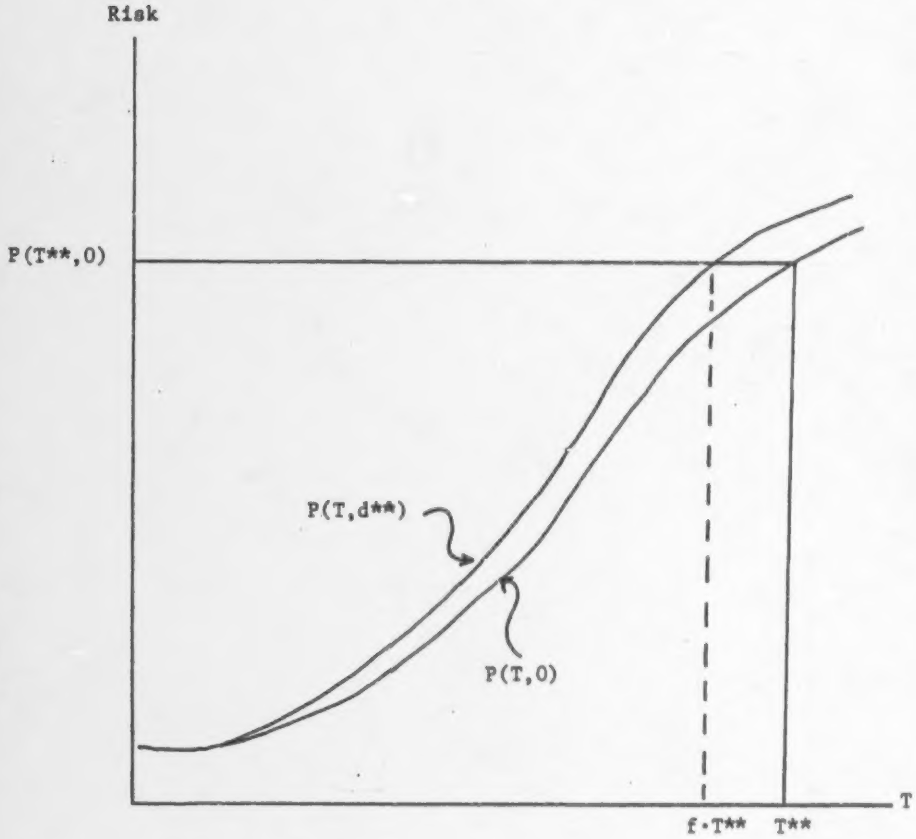
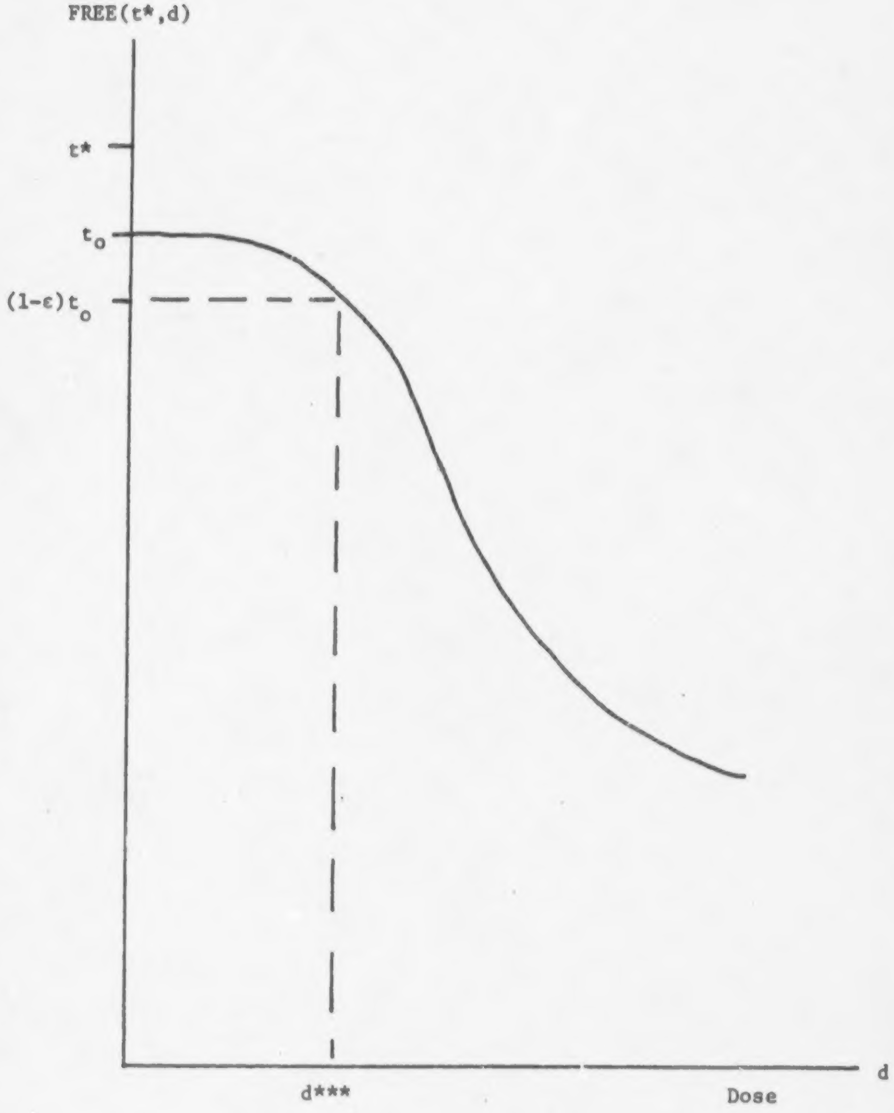


Figure 4 The Definition of the Mean Free Dose d***



## 4.9 The Estimation of Carcinogenic Risk

The restricted maximum likelihood estimates of the model parameters are denoted herein by $\hat{\alpha}$, $\hat{\beta}$, and possibly either $\hat{\gamma}$ or $\hat{\phi}$. The restricted maximum likelihood estimate of the model $P(T,d)$ is formed by replacing the unknown parameters $(\alpha,\beta,\gamma,\phi)$ in $P(T,d)$ by their corresponding restricted maximum likelihood estimates $(\hat{\alpha},\hat{\beta},\hat{\gamma},\hat{\phi})$ and is denoted by $\hat{P}(T,d)$. The restricted maximum likelihood estimation procedure is discussed in Section 4.6.

Once the restricted maximum likelihood estimate of the model is obtained, there is a straightforward procedure to obtain "best estimates" (restricted maximum likelihood estimates) of risk. The best estimate of a particular virtually safe dose is the smallest $d > 0$ satisfying

$$\pi = \hat{P}(T^*,d) - \hat{P}(T^*,0) \tag{4.9.1}$$

in analogy with the definition (4.8.1) of a virtually safe dose and is denoted by $\hat{d}^*$. The best estimate of a particular late risk dose is the smallest $d > 0$ satisfying

$$\hat{P}(T^{**},0) = \hat{P}(f \cdot T^{**},d) \tag{4.9.2}$$

in analogy with the definition (4.8.2) of a late risk dose and is denoted by $\hat{d}^{**}$. The best estimate of a particular mean free dose is the smallest $d > 0$ satisfying

$$\frac{\text{FREE }(T^{***},d)}{\text{FREE }(T^{***},0)} \geq 1 - \varepsilon \tag{4.9.3}$$

in analogy with the definition of a mean free dose (4.8.6) and is denoted by $\hat{d}^{***}$. The best estimate of the probability of a positive response by time T at dose level d is $\hat{P}(T,d)$. In fact, if $\xi$ is some quantity defined in terms of $P(T,d)$, then the best estimate of $\xi$ is $\hat{\xi}$ obtained by replacing $P(T,d)$ by $\hat{P}(T,d)$ in the definition of $\xi$. Therefore, best estimates $\hat{\xi}$ of such $\xi$ are easily obtained from $\hat{P}(T,d)$.

Confidence limits or intervals can also be obtained on any quantity $\xi$ defined in terms of $P(T,d)$. Such 95% confidence intervals, say $[L,U]$, on $\xi$ have the property that

$$P(L \leq \xi \leq U) = .95 \quad . \tag{4.9.4}$$

A 95% lower confidence limit, say $\xi_L$, on $\xi$ has the property that

$$P(\xi_L \leq \xi) = .95 \quad . \tag{4.9.5}$$

Similarly a 95% upper confidence limit, say $\xi_U$, on $\xi$ has the property that

$$P(\xi \leq \xi_U) = .95 \quad . \tag{4.9.6}$$

The intervals $[L,U]$, $[\xi_L,\infty)$, and $(-\infty\ ,\ \xi_U]$ are all random intervals which have a specified probability of containing the specified $\xi$.

Let $\xi$ denote the risk characteristic of interest. Let $\hat{\xi}$ denote the restricted maximum likelihood estimate of $\xi$. All of the available experimental (simulated) data is used in determining $\hat{\xi}$. This group of data is considered to be the first group, $g = 1$, and $\hat{\xi}_1 = \hat{\xi}$. Then $G - 1$ additional groups, $g = 2, 3, \ldots, G$ are simulated. All G groups of data are used to determine confidence limits on $\xi$.

The G - 1 additional groups ($g = 2, 3, \ldots, G$) are all replicates of the original experiment, $g = 1$; i.e., the groups $g = 2, 3, \ldots, G$ have the same dose levels and numbers of experimental units per dose level as in the original group, $g = 1$. The observations in the g-th group ($g \geq 2$) at a particular dose level d are generated by MRS. T 1981 by randomly sampling (with replacement) the observations at dose level d in the original experiment. By considering each of the G groups individually, G separate restricted maximum likelihood estimates ($\hat{\xi}_g$, $g = 1, 2, \ldots, G$) of $\xi$ are obtained.

Two procedures are considered herein for determining a $\xi_L$ such that

$$P(\xi_L \leq \xi) \doteq .95 \quad . \tag{4.9.7}$$

These two 95% lower confidence limits $\xi_L$ on $\xi$ are denoted by $\xi_{L,t}$ and $\xi_{L,\min}$.

The first lower confidence limit $\xi_{L,t}$ uses the additional G - 1 groups ($g = 2, 3, \ldots, G$) only to provide information about the statistical variability of $\hat{\xi}$ . Assuming a t-distribution with G - 1 degrees of freedom for

$$(\log \hat{\xi} - \log \xi)/s_{\hat{\xi}} \tag{4.9.8}$$

where

$$s_{\hat{\xi}}^2 = [G-1]^{-1} \sum_{g=1}^{G} \{\log \hat{\xi}_g - [G^{-1} \sum_{g=1}^{G} \log \hat{\xi}_g]\}^2 \quad , \tag{4.9.9}$$

a 95% lower confidence limit, $\hat{\xi}_L$, on $\xi$ is given by

$$\hat{\xi}_L = \exp \{\log \hat{\xi} - s_{\hat{\xi}} \cdot t_{.95,G-1}\} \tag{4.9.10}$$

where $t_{.95,G-1}$ is the 95-th percentile of a t-distribution with G-1 degrees of freedom. Of course, the 95% could be replaced by another specified percentage. The robustness of the t-distribution used in determining $\hat{\xi}_L$ is well known. An empirical justification is given in Hartley and Sielken (1977b). In particular the empirical study indicated a good fit for the t-distribution when $\alpha_1$ in P(T,d) was significantly positive, $\alpha_1 >> 0$. As $\alpha_1$ approached 0, the tendency was for $\hat{\xi}_L$ to underestimate $\xi$ slightly more.

The second lower confidence limit $\xi_{L,\min}$ makes no assumptions concerning the shape of the distribution of the best estimate $\hat{\xi}$. The only assumption made is that for each g = 1, ... G $\hat{\xi}_g$ has a 50-50 chance of being above or below $\xi$; i.e.,

$$P(\hat{\xi}_g \leq \xi) = .5 \quad . \tag{4.9.11}$$

Then, the probability that the minimum of $\hat{\xi}_1, \hat{\xi}_2, \ldots, \hat{\xi}_G$ is less than or equal to $\xi$ is

$$P(\min\{\hat{\xi}_1, \hat{\xi}_2, \ldots, \hat{\xi}_G\} \leq \xi) \doteq 1 - (.5)^G \tag{4.9.12}$$

The probability would be exactly $1-(.5)^G$ if the $\hat{\xi}_1, \ldots, \hat{\xi}_G$ were independent. For G = 5

$$P(\min\{\hat{\xi}_1, \hat{\xi}_2, \ldots, \hat{\xi}_G\} \leq \xi) \doteq 1 - (.5)^G \doteq .97 \tag{4.9.13}$$

Thus, the minimum of $\hat{\xi}_1, \hat{\xi}_2, \ldots, \hat{\xi}_5$ can be used as an approximate 95% lower confidence limit on $\xi$.

It is important to note that the additional G-1 groups used in determining the confidence limits for the $\xi$ are generated directly from the original data and not from $\hat{P}(T,d)$. Thus, the confidence limits reflect the statistically variability in $\hat{\xi}$ and do not presume that the estimated model $\hat{P}(T,d)$ is actually the exact underlying model.

It is also important to note that MRS. T 1981 does not calculate what would be called a lower fiducial limit, $\xi_L$, by the following two step procedure:

(i) Determine the region in the parameter space for which the likelihood, L, satisfied $L(\alpha,\beta,\gamma,\phi) \geq qL(\hat{\alpha},\hat{\beta},\hat{\gamma},\hat{\phi})$ (where $0 < q < 1$).

(ii) Determine $\xi$ for all $\alpha,\beta,\gamma,\phi$ in this region and let $\xi_L$ be the smallest of these $\xi$.

Peto and Mantel (private communications) report that with this method lower limits for $\xi$ are virtually invariant to the levels of the $\alpha_i$ for $i \geq 2$. Instead MRS. T 1981 essentially sets up the maximum likelihood estimate of the only relevant parametric function of $(\alpha,\beta,\gamma,\phi)$ namely $\xi$. If a sufficient statistic for this parametric function were known which would be independent of nuisance parameters, this statistic would be the appropriate basis for determining $\xi_L$. MRS. T 1981 attempts an approximation to this latter procedure.

The general Hartley-Sielken model does not assume prior to the data analysis either a linear or nonlinear shape when it is used to fit observed data. Nor does the confidence limit procedure implementation in MRS. T 1981 assume prior to the data analysis any linearity or nonlinearity. On-the-other-hand several other commonly used confidence limit procedures which make asymptotic normality assumptions do assume that the model is linear in the low dose region. This makes those lower confidence limits suspect since they may greatly underestimate the true quantity when the true model is nonlinear in the low dose region.

## 5. Risk Assessment Using MRS. T 1981

To do risk assessment using MRS. T 1981, the user must, of course, tell MRS. T 1981 (1) what data is to be considered; (2) what descriptions of the data are to be produced; (3) which form of the Hartley-Sielken model is to be used; (4) what initial information, if any, is available about the parameters in the Hartley-Sielken model; (5) which of the many implications of the fitted model are to be tables; etc. In this section the specific capabilities of MRS. T 1981 and the many options available to the program user are discussed. The discussion is subdivided into the following subsections:

5.1 The User's Description of his Experiment and his Experimental Data

5.2 Simple Descriptions Generated by MRS. T 1981 of the Experimental Data

5.3 The Forms of the Hartley-Sielken Model Which Can Be Fit to the Data

5.4 The Procedures for Estimating the Hartley-Sielken Model Parameters

5.5 The Goodness-of-Fit of the Estimated Hartley-Sielken Model to the Experimental Data

5.6 Risk Characterizations Provided by MRS. T 1981

5.7 Simulation Capabilities

Section 6 indicates the specific input instructions for using MRS. T 1981. These instructions are summarized in Appendix A and illustrated by examples in Appendix B. Hence the purpose of this section is to indicate to the user just what MRS. T 1981 can do, what the user's options are, and what information the user must supply.

## 5.1 The User's Description of his Experiment and his Experimental Data

MRS. T 1981 will perform analyses on experimental data or, if requested, simulate data from a specified model and perform analyses on the simulated data. In subsections 5.1 - 5.6 the discussion is phrased primarily in terms of experimental data. Basically only the terminology would change if instead simulated data were being analyzed. Simulation is discussed extensively in subsection 5.7.

The first input card is simply any title or label the user wants to have printed at the beginning of the program output. The purpose of the title is only to distinquish one analysis from another.

The description of experimental data begins with the number, D, of dose levels and the specification of the values of the dose levels, $d_1$, $d_2$, ..., $d_D$. For example,

$$d_1 = 0.0 \ ,$$

$$d_2 = 1.3 \ ,$$

$$d_3 = 2.6 \ ,$$

$$d_4 = 3.9 \ ,$$

$$d_5 = 5.1 \ ,$$

and

$$D = 5 \ .$$

The first dose level must always be $d_1 = 0.0$ even if no observations are to be read in or simulated at this dose level. The remaining dose levels, $d_2$, $d_3$, ..., $d_D$, should be positive and in ascending

Let $n_i$ denote the number of experimental units (animals) at dose $d_i$. Then, the values of $n_1$, $n_2$, ..., $n_D$ are read in next. Of course, the $n_i$'s do not all have to be equal. Presumable the only time no observations would be read in or simulated at the zero dose level (i.e. $n_1 = 0$) is when there is prior knowledge that a response cannot occur when $d = 0$. Thus, if there are no observations at $d_1 = 0.0$, the program assumes that the probability of not having a positive response by time T when $d = 0$ is zero; i.e., $P(T,0) = 0$.

Once the dose levels and numbers of experimental units per dose level have been read in, the number, G-1, of additional groups to be simulated is supplied. If $G-1 = 0$ and hence $G=1$, then no confidence limits will be determined. (See Section 4.9 concerning the determination of confidence limits.)

The actual experimental observations are the last information read in to MRS. T 1981. However, we shall jump ahead and discuss the input of experimental observations now.

The first of the two possible formats for inputting the experimental observations is to read in each observation separately. First would come $n_1$ cards for dose level $d_1$ ($d_1 = 0$), then $n_2$ cards for the smallest positive dose level $d_2$, and so forth until finally $n_D$ cards for the highest dose level $d_D$. Each card would contain (i) the "type" of the observation and (ii) the observation time (time of response, death, sacrifice, etc.). The term "type" is used herein as follows:

Type 1 implies that a positive response has occurred at the observation time.

Type 2 implies that a positive response has occurred but it is only known that the positive response occurred sometime either at or before the observation time, and

Type 3 implies that a positive response has not occurred by the observation time.

The second of the two formats for inputting the experimental observations is usually more convenient than the first format if there are several animals with the same observation time. The cards for $d_1$ precede those for $d_2$, etc. For animals at a particular dose level there would be one card containing the number of distinct observation times for these animals and then for each of these distinct observation time there would be a card indicating the observation time itself, as well as how many observations were of type 1, how many observations were of type 2, and how many observations were of type 3.

## 5.2 Simple Descriptions Generated by MRS. T 1981 of the Experimental Data

After the data has been either read in or simulated the user may have any of several simple descriptions printed. These descriptions refer only to the data itself and no modelling thereof.

If the user wants, the program will print a Table A.1 containing the original observations comprising group 1 (g=1) exactly as they were read in or simulated as well as the observations in the additional groups (g = 2, 3, ..., G). Table A.1 is intended to help the user make sure that the data in group 1 to be analyzed by the program is in fact the data he wanted to analyze. Table A.1 also provides a complete record of the data underlying the information produced by the program.

If the user wants, the program will print a Table A.2 containing the number and percentage of observations of types 1, 2, and 3 for each group. If requested, Table A.3 will contain a more detailed breakdown of the information in Table A.2 and list the number and percentage of observations of types 1, 2, and 3 for each dose level within each group. Finally, if requested, Table A.4 will contain the observed proportion of positive responses by specified times T for each dose level. If Table A.4 is requested, the user will have to input the specified times T to appear in Table A.4. Table A.4 can be printed for each group separately, or Table A.4 can be printed only for the first group.

If the user so requests, Table A.5 will indicate the observed minimum Type 1 or 2 response time for each dose level for each group.

Generally all descriptive tables (except tables of lower confidence limits) can be either (i) not printed, (ii) printed only for the first group, or (iii) printed for each group separately.

## 5.3 The Forms of the Hartley-Sielken Model Which Can Be Fit to the Data

Any one of several possible forms of the Hartley-Sielken model can be fit to the data. These forms are all special cases of

$$P(T,d) = P(T,d;\alpha,\beta,\delta)$$

$$= 1 - \exp\{-g(d;\alpha)H[T;\beta,\delta(d)]\} \qquad (5.3.1)$$

where

$$g(d;\alpha) = \sum_{s=0}^{a} \alpha_s d^s . \qquad (5.3.2)$$

The user must specify the maximum degree, a, in the polynomial $g(d;\alpha)$. The user may specify initial estimates of the $\alpha$'s or may require the program to compute its own initial estimates. The final estimate of $\alpha$ will be denoted herein as $\hat{\alpha}$. The user may require $g(d;\hat{\alpha})$ to be nondecreasing in d in which case all of the estimated $\alpha$'s will be nonnegative; i.e.

$$\hat{\alpha}_s \geq 0, \; s = 0, \ldots, a . \qquad (5.3.3)$$

In any case the estimated $\alpha$'s will always make

$$g(d;\hat{\alpha}) \geq 0 \qquad (5.3.4)$$

for all dose levels d such that $0 \leq d \leq d_D$ .

There are essentially three possible general forms for $H[T;\beta,\delta(d)]$; namely,

$$H[T;\beta,\delta(d)] = H(T;\beta) \qquad (5.3.5)$$

in which case $\delta(d) \equiv 0$ for all d,

$$H[T;\beta,\delta(d)] = H(T;\beta) - \delta(d) \tag{5.3.6}$$

in which case $\delta(d)$ plays the role of $\gamma(d)$ in Section 4.4, and

$$H[T;\beta,\delta(d)] = H[T - \delta(d);\beta] \tag{5.3.7}$$

in which case $\delta(d)$ plays the role of $\phi(d)$ in Section 4.5. For both $\delta(d) = \gamma(d)$ and $\delta(d) = \phi(d)$, the function $\delta(d)$ is treated nonparametrically in the sense that

$$\delta_1 = \delta(d_1),\ \delta_2 = \delta(d_2),\ \ldots,\ \delta_D = \delta(d_D)$$

are each estimated separately and no functional form is assumed for $\delta(d)$. In any of (5.3.5) - (5.3.7) the $H(t;\beta)$, with $t = T$, T, or $T - \delta(d)$ respectively, can be of either of two forms; namely,

$$H(t;\beta) = \sum_{r=1}^{b} \beta_r t^r \tag{5.3.8}$$

or

$$H(t;\beta) = \sum_{r=1}^{b} \beta_r\, \theta_r(t) \tag{5.3.9}$$

where

$\theta_r(t) =$ either $\ell n(t + 1)$, $e^t - 1$, or a
specified power of t .

In both (5.3.8) and (5.3.9) the user must specify b. The user may specify initial estimates of $\beta_1, \ldots, \beta_b$ or let the program compute its own initial estimates. If $\delta(d)$ is not specified to always be 0, then the user may specify initial estimates of

$$\delta_1 = \delta(d_1),\ \delta_2 = \delta(d_2),\ \ldots,\ \delta_D = \delta(d_D) \tag{5.3.10}$$

or let the program compute its own initial estimates.

The final estimates of the $\beta$'s and $\delta$'s are denoted by $\hat{\beta}$ and $\hat{\delta}$ respectively herein. Regardless of the form of $H[T;\beta,\delta(d)]$, the estimates $\hat{\alpha}$, $\hat{\beta}$, and $\hat{\delta}$ are always chosen so that $\hat{P}(T,d) = P(T,d;\hat{\alpha},\hat{\beta},\hat{\delta})$ is a distribution function in T. Specifically, $\hat{P}(T,d)$ is $\geq 0$ and nondecreasing in T for all T's in the observed range of T values. Furthermore $\hat{P}(T,d)$ tends to 1.0 as T increases.

Since there is an arbitrary scale factor between $g(d;\hat{\alpha})$ and $H[T;\hat{\beta},\hat{\delta}(d)]$, the $\hat{\beta}$'s are required to satisfy

$$\hat{\beta}_r \geq 0,\ r = 1, \ldots, b \tag{5.3.11}$$

and without loss of generality satisfy

$$\sum_{r=1}^{b} \hat{\beta}_r = 1 \ . \tag{5.3.12}$$

The $\hat{\delta}$'s are chosen so that

$$\hat{\delta}_i \geq 0\ ,\ i = 1, 2, \ldots, D\ . \tag{5.3.13}$$

If $\delta(d)$ is playing the role of $\gamma(d)$, then

$$H(T;\hat{\beta}) - \hat{\delta}(d) \geq 0 \tag{5.3.14}$$

for all T's $\geq$ observed minimum Type 1 or 2 response time at dose level d and

$$H[T;\hat{\beta},\hat{\delta}(d)] \equiv \max\{0,\ H(t;\hat{\beta})-\hat{\delta}(d)\} \tag{5.3.15}$$

for all T. If $\delta(d)$ is playing the role of $\phi(d)$, then

$$T - \hat{\delta}(d) \geq 0 \tag{5.3.16}$$

for all T's $\geq$ observed minimum Type 1 or 2 response time at dose level d and

$$H[T;\hat{\beta},\hat{\delta}(d)] \equiv \max\{0, H[T-\hat{\delta}(d);\hat{\beta}]\} \tag{5.3.17}$$

for all T.

Appendix C describes how the program, if requested, determines its own initial estimates of the $\alpha$'s, $\beta$'s, or $\delta$'s.

## 5.4 The Procedures for Estimating the Hartley-Sielken Model Parameters

The parameters in the Hartley-Sielken model are the $\alpha$'s, $\beta$'s, and $\delta$'s. These parameters are usually estimated by the program. Maximum likelihood estimation is used with the parameter estimates restricted as discussed in subsection 5.3. The estimation process is a sequential simultaneous search beginning at initial parameter estimates which have either been user supplied or determined by MRS. T 1981 herself. Basically, once the user has decided on the form of the model as discussed in subsection 5.3 and made his decisions concerning the initial parameter estimates, the program does all the work and the user has no further decisions concerning the estimation process itself.

The user may, however, specify fixed values for the $\beta$'s and/or $\delta$'s and thereby eliminate these parameters from the estimation process. Fixing $\delta \equiv 0$ eliminates the $\gamma$'s and $\phi$'s from the Hartley-Sielken model. The capability to fix $\delta \not\equiv 0$ and/or fix the $\beta$'s is included solely for research purposes. Fixing $\delta \not\equiv 0$ and/or fixing the $\beta$'s should not be done under normal circumstances.

MRS. T 1981 can provide considerably more information than just the restricted maximum likelihood estimates of the $\alpha$'s, $\beta$'s, and $\delta$'s. Hence, sometimes the user may find that he has his estimates of the $\alpha$'s, $\beta$'s, and $\delta$'s - presumably from a previous run of the program - but now he wants some of the other information MRS. T 1981 can provide. For this reason the user may specify that MRS. T 1981 skip the estimation of the $\alpha$'s, $\beta$'s, and $\delta$'s entirely and simply use estimates of the $\alpha$'s, $\beta$'s, and $\delta$'s supplied by the user. Of course, if there are more than one group ($G > 1$) and the estimation process is to be skipped entirely, the user must supply the $\alpha$'s, $\beta$'s, and $\delta$'s for $g = 1, 2, \ldots, G$.

The restricted maximum likelihood estimation of $\alpha$, $\beta$, and $\gamma$ is done separately for each group $g = 1, \ldots, G$ yielding $\hat{\alpha}(g) = [\hat{\alpha}_0(g), \ldots, \hat{\alpha}_a(g)]$, $\hat{\beta}(g) = [\hat{\beta}_1(g), \ldots, \hat{\beta}_b(g)]$, and $\hat{\delta}(g) = [\hat{\delta}_1(g), \ldots, \hat{\delta}_D(g)]$.

For information purposes the sample means

$$\bar{\alpha}_s = \sum_{g=1}^{G} \hat{\alpha}_s(g)/G \ , \qquad s = 0, 1, \ldots, a \ ,$$

$$\bar{\beta}_r = \sum_{g=1}^{G} \hat{\beta}_r(g)/G \ , \qquad r = 1, 2, \ldots, b \ ,$$

$$\bar{\delta}_d = \sum_{g=1}^{G} \hat{\delta}_d(g) \ , \qquad d = 1, 2, \ldots, D$$

and the sample standard deviations of these means

$$s_{\bar{\alpha}_s} = \{ \sum_{g=1}^{G} [\hat{\alpha}_s(g) - \bar{\alpha}_s]^2/G(G-1)\}^{\frac{1}{2}} \ ,$$

$$s_{\bar{\beta}_r} = \{ \sum_{g=1}^{G} [\hat{\beta}_r(g) - \bar{\beta}_r]^2/G(G-1)\}^{\frac{1}{2}} \ ,$$

$$s_{\bar{\delta}_d} = \{ \sum_{g=1}^{G} [\hat{\delta}_d(g) - \bar{\delta}_d]^2/G(G-1)\}^{\frac{1}{2}}$$

are always printed.

### 5.5 The Goodness-of-Fit of the Estimated Hartley-Sielken Model to the Experimental Data

The Hartley-Sielken model can often fit the data fairly well. This can be seen by comparing the observed and predicted responses. In making these comparisons it should be remembered that the Hartley-Sielken model is not fit separately for each dose level nor fit separately for each time but rather must simultaneously fit all dose levels and all times.

At a particular dose d the carcinogen is acting in such a way that a proportion, $\rho(t,d)$, of the population would develop a response at a time t. The probability that a response would develop by time T is

$$P(T,d) = \int_{o}^{T} \rho(t,d)\,dt \quad ;$$

that is, $P(T,d)$ is the cumulative frequency of times to response before T. The Hartley-Sielken model estimates the cumulative frequency $P(T,d)$ by $\hat{P}(T,d)$.

There is considerable information about the cumulative frequency $P(T,d)$ in the data. However, when the time of response is not always directly observable and sometimes only the presence or absence of a response in a necropsy is observable, there is no simple sample proportion utilizing the majority of the sample information to compare to $\hat{P}(T,d)$. In MRS. T 1981 two characterizations of what was observed can be compared to the predicted responses.

The simplest characterization is based directly on the number of animals which were observed (sacrificed, etc.) during a particular time period and had a positive necropsy (i.e., had a response of the type being considered). Let $T_0 = 0 < T_1 < T_2 < \ldots < T_M < T_{M+1} = \infty$ be specified times such that the time periods

$$[0,T_1],\ (T_1,T_2],\ \ldots,\ (T_{M-1},T_M],\ (T_M,\infty) \qquad (5.5.1)$$

are of interest to the user. Let

$n(i,d)$ = the number of animals at dose d that were observed during the period $(T_{i-1},T_i]$ and

$p(i,d)$ = the proportion of these $n(i,d)$ animals that had a positive necropsy.

Then, for $m = 1, 2, \ldots, M + 1$,

$$\mathrm{OBS}(T_m,d) = \sum_{i=1}^{m} n(i,d)p(i,d) \qquad (5.5.2)$$

is the observed number of animals at dose d that were necropsied before $T_m$ and had a positive necropsy. The predicted quantity analogous to $\mathrm{OBS}(T_m,d)$ is

$$\mathrm{PRED}(T_m,d) = \sum_{i=1}^{m} n(i,d)P(i,d). \qquad (5.5.3)$$

Thus $\mathrm{OBS}(T_m,d)$ and $\mathrm{PRED}(T_m,d)$ are the cumulative observed and predicted numbers of animals at dose d with positive necropsies by $T_m$. Both $\mathrm{OBS}(T_m,d)$ and $\mathrm{PRED}(T_m,d)$ are nonnegative and are nondecreasing as m increases. The magnitude of the difference between $\mathrm{OBS}(T_m,d)$ and $\mathrm{PRED}(T_m,d)$ should be relatively small for all $T_m$. Let $S_d$ be the total number of experimental units under consideration at dose level d; thus $S_d$ is the number of experimental units at dose level d in either a particular group or the combination of all groups. Then the user may specify M and $T_1, \ldots, T_M$ and have MRS. T 1981 print Table B.1 containing $OBS(T_m,d)/S_d$ and $PRED(T_m,d)/S_d$ for $m = 1, 2, \ldots, M + 1$ and each experimental dose level d. Table B.1 will also include

$$OBS(T_m) = \sum_d OBS(T_m,d) \qquad (5.5.4)$$

and

$$PRED(T_m) = \sum_d PRED(T_m,d) \qquad (5.5.5)$$

each divided by $\sum_d S_d$ .

A goodness-of-fit statistic can be constructed using quantities analogous to $OBS(T_m,d)$, $OBS(T_m)$, $PRED(T_m,d)$ and $PRED(T_m)$. Let M* and $T_0{}^* = 0 < T_1{}^* < T_2{}^* < \ldots < T^*_{M^*} < T^*_{M^*+1} = \infty$ be specified by the user. Then

$$\chi^2_d(1) = \sum_{m=1}^{M^*+1} \{[OBS(T^*_m,d)-OBS(T^*_{m-1},d)]-[PRED(T^*_m,d)-PRED(T^*_{m-1},d)]\}^2/ \\ [PRED(T^*_m,d)-PRED(T^*_{m-1},d)] \qquad (5.5.6)$$

for all experimental doses d and

$$\chi^2(1) = \sum_d \chi^2_d(1) \qquad (5.5.7)$$

should be small if the estimated Hartley-Sielken model is a good fit to the data. If $T_1{}^* < \ldots < T^*_{M^*}$ are specified so that the expected number of responses in each period $(T^*_{m-1}, T^*_m]$ is at least 5 (i.e. $PRED(T^*_m,d)-PRED(T^*_{m-1},d) \geq 5$) for each experimental dose level d, then $\chi^2_d(1)$ and $\chi^2(1)$ can be compared with the upper percentiles of a chi-squared distribution with M* and D·M* degrees of freedom respectively and approximate goodness-of-fit tests obtained. If the user specifies M* and $T_1^*, \ldots, T_{M*}^*$, then $\mathrm{OBS}(T_m^*,d)$, $\mathrm{PRED}(T_m^*,d)$, $\chi_d^2(1)$, and $\chi^2(1)$ will appear in Table B.2.

The desire to have $\mathrm{PRED}(T_m^*,d)-\mathrm{PRED}(T_{m-1}^*,d) \geq 5$ for all m and experimental doses d will usually necessitate making M* fairly small and $T_1^* < \ldots < T_{M*}^*$ a fairly coarse partition so that $(T_{m-1}^*,T_m^*]$ is sufficiently large. The user dose not have to make $T_1^*, \ldots, T_{M*}^*$ equally spaced. Usually M would be chosen greater than M*. Either Table B.1 or Table B.2 or both can be requested.

In the above comparisons and Table B.1 and B.2 OBS(T,d) and OBS(T) only reflect those animals that were observed before T. They ignore all observations after T even though the animals observed after T do convey some information about the risk before T. For instance, an animal that has a negative necropsy at some time after T would also have had a negative necropsy at any time $\leq$ T. The desire to include all of the sample information in the comparison of observed and predicted responses leads to the following second way of computing the "observed count" of the number of animals which developed a response by time T. Let t denote the time at which the carcinogen causes or would cause a response to develop. Let $\tau$ denote the time the animal is observed - the time of death, sacrifice, etc. If the necropsy indicates the presence of a response ($t \leq \tau$), then the contribution to the count is

(a) 1 if $\tau \leq T$, and
(b) $P(t \leq T \text{ given } t \leq \tau)$ if $\tau > T$ (5.5.8)

where $P(t \leq T \text{ given } t \leq \tau)$ is the conditional probability that the response occurred before T, $(t \leq T)$, when it is only known that the response did occur before $\tau$, $(t \leq \tau)$. If the necropsy indicates the absence of a response $(t > \tau)$, then the contribution to the count is

$$\begin{aligned} &\text{(a)}\quad 0 \text{ if } \tau \geq T, \text{ and} \\ &\text{(b)}\quad P(\tau < t \leq T \text{ given } t > \tau) \text{ if } \tau < T \end{aligned} \qquad (5.5.9)$$

where $P(\tau < t \leq T \text{ given } t > \tau)$ is the conditional probability that the response would have occurred between $\tau$ and T, $(\tau < t \leq T)$, when it is only known that the response did not occur before $\tau$, $(t > \tau)$. The inclusion of the conditional probabilities makes the count reflect all the animals. Since the exact conditional probabilities are unknown, the "observed counts" are computed as in (5.5.8) and (5.5.9) with the exact conditional probabilities replaced by their estimates from $\hat{P}(T,d)$. If the user so requests and M and $T_1 < \ldots < T_M$ are specified, then in Table B.3 for each experimental dose d MRS. T 1981 will print $\hat{P}(T_m,d)$ and the corresponding "observed proportion" - where the "observed proportion" is the above "observed count" divided by the total number, $S_d$, of experimental units under consideration at dose level d.

Table B.3 provides a second comparison of the observed and predicted behavior. Table B.3 does require a non-trivial amount of computer time to generate and hence should be requested only if really wanted.

Goodness-of-fit statistics analogous to those in Table B.2 but using the above "observed counts" can be requested and would appear in Table B.4.

The M and $T_1$, ..., $T_M$ are the same for Table B.1 and B.3; also, the M* and $T_1$*, ..., $T^*_{M^*}$ are the same for Table B.2 and Table B.4. Of course, Table B.3 and Table B.4 or both can be requested regardless of requests concerning Tables B.1 and B.2.

## 5.6 Risk Characterizations Provided by MRS. T 1981

Once the restricted maximum likelihood estimates $\hat{\alpha}$, $\hat{\beta}$, $\hat{\delta}$ of the model parameters have been obtained, there is a great deal of information that can be obtained from

$$\hat{P}(T,d) = P(T,d;\ \hat{\alpha},\hat{\beta},\hat{\delta}) \quad . \qquad (5.6.1)$$

This information is subdivided into Tables C.1 - C.3 which refer to general implications of $\hat{P}(T,d)$ and Tables VSD.1 - VSD.5, LRD.1 - LRD.5, and MFD.1 - MFD.5 which refer to possible definitions of an "acceptable" dose level.

Table C.1, if requested, shows the estimated probability, $\hat{P}(T,d)$, of a response at each specified time T for each specified dose d. If the user requests Table C.1, the user must specify the times T and dose levels d to be considered in the table. The times T must be equally spaced. There is no restriction on the dose levels d.

Table C.2, if requested, shows the estimated time T corresponding to a specified probability of a response at a specified dose d; that is, the time T for $\hat{P}(T,d)$ to reach a specified risk level for a given dose level d. If the user requests Table C.2, the user must specify the dose levels of interest as well as the risk levels themselves.

Table C.3, if requested, shows the estimated response free period at specified doses for specified maximum periods. Thus, if the user specifies a maximum period length equal to t, then Table C.3 will indicate for each specified dose level the expected length of time in the interval [0,t] which will be free of response. If the user requests Table C.3, then the user must specify the maximum period lengths and the dose levels to be considered.

In subsection 4.8 three definitions of an acceptable risk were discussed. These three definitions gave rise to three definitions of an "acceptable" dose level; namely, the current "virtually safe dose" which is abbreviated to VSD or $d^*$ and is defined in (4.8.1), the new "late risk dose" which is abbreviated to LRD or $d^{**}$ and is defined in (4.8.2), and the new "mean free dose" which is abbreviated to MFD or $d^{***}$ and is defined in (4.8.6). Let $\xi$ represent the true "acceptable" dose level. Then $\hat{\xi}$ is the best estimate of $\xi$ based on $\hat{P}(T,d)$, and $\hat{\xi}_L$ is the lower confidence limit on $\xi$ discussed in subsection 4.9.

For each of the three possible definitions of $\xi$, the user may request any of five tables (Tables VSD.1 - VSD.5, Tables LRD.1 - LRD.5, Tables MFD.1 - MFD.5). In general terms the five possible tables would show

Table $\xi$.1 : $\hat{\xi}$
Table $\xi$.2 : $\hat{\xi}_L$
Table $\xi$.3 : $\hat{\xi}/\hat{\xi}_L$
Table $\xi$.4 : $\hat{\xi}/\xi$
Table $\xi$.5 : $\hat{\xi}_L/\xi$ .

Of course, Tables $\xi$.4 and $\xi$.5 can only be requested if simulated data is being considered since only then can $\xi$ be determined.

Naturally, whenever the user requests tables for a particular $\xi$, the user must specify the parameters in the definition of $\xi$. For the VSD the parameters in (4.8.1) are $\pi$ and $T^*$. For the LRD the parameters in (4.8.2) are $f$ and $T^{**}$. For the MFD the parameters in (4.8.6) are $\varepsilon$ and $T^{***}$. If the user requests tables involving the lower confidence limit $\hat{\xi}_L$, the user must specify whether the confidence level is to be 90%, 95%, or 99%.

## 5.7 Simulation Capabilities

MRS. T 1981 can simulate data for research purposes as well as analyze real experimental data. Since any analysis which can be requested for experimental data can also be requested for the simulated data, this subsection will focus on only the simulation of the data itself.

The following parameters of the simulation study are specified in exactly the same manner as they are specified for experimental data:

(i) the number of dose levels, D;

(ii) the values of the dose levels, $d_1, d_2, \ldots, d_D$;

(iii) the number of additional groups, G-1; and

(iv) the number of experimental units observed at the i-th dose level, $n_i$, $i = 1, \ldots, D$.

When the behavior of an individual experimental unit is simulated, the following 4 times are of interest:

(i) t, the time at which a response would occur;

(ii) $\tau$, the time death would occur if death is specified as a "competing risk";

(iii) TSACR, the time of sacrifice if serial sacrifices are specified; and

(iv) TTERM, the time at which the experiment is terminated; i.e., the maximum length of time on experiment.

Any of $\tau$, TSACR, and TTERM can be conceptualized as being infinite if the corresponding cause for observing the animal at that time is not to be considered. Let TOBS denote the time of observation of the experimental unit; i.e., TOBS is the one time at which the presence or absence of a response is to be observed and recorded.

If the time, t, at which a response occurs can be detected immediately when the response occurs and detection does not have to wait for death or sacrifice, then

$$\mathrm{TOBS} = \min\{t, \tau, \mathrm{TSACR}, \mathrm{TTERM}\} \ . \qquad (5.7.1)$$

If in (5.7.1)

$$t = \mathrm{TOBS} \ , \qquad (5.7.2)$$

then the observation is designated as a Type 1 observation which means that a response occurred and was detected immediately. If in (5.7.1)

$$t > \mathrm{TOBS} \ , \qquad (5.7.3)$$

then the observation is designated as Type 3 which means that a response did not occur before the experimental unit was observed.

If the time, t, at which a response occurs cannot be detected immediately and detection must wait until the experimental unit is observed at the time of death or sacrifice, then

$$\mathrm{TOBS} = \min\{\tau, \mathrm{TSACR}, \mathrm{TTERM}\} \ . \qquad (5.7.4)$$

If

$$t \leq \mathrm{TOBS} \ , \qquad (5.7.5)$$

then the observation is designated as a Type 2 observation which means that a response occurred sometime before TOBS but the exact time of occurrence is unknown. If

$$t > \text{TOBS} \quad , \tag{5.7.6}$$

then the observation is designated as a Type 3 observation.

The time, t, to response can be generated from any of the following six cumulative distribution functions where P(T,d) denotes the probability that $t \leq T$ when the experimental unit is at dose level d:

(1) $$P(T,d)=1.0-\exp\{-g(d,\text{WALPHA})*H[T,\text{TRUEK},\text{WBASE}(d)]\} \tag{5.7.7}$$

where

$$g(d,\text{WALPHA})=\sum_{s=1}^{\text{LTRUE}+1} \text{WALPHA}(s)*d^{s-1} \quad ,$$

$$H[T,\text{TRUEK},\text{WBASE}(d)]=[T-\text{WBASE}(d)]^{\text{TRUEK}} \quad ,$$

and

WBASE(d)=WBASE(i) if d is the i-th smallest dose level;

(2) $$P(T,d)=1-\exp\{-g(d,\text{WALPHA})*H(T,\text{WBETA})\} \tag{5.7.8}$$

where

$$g(d,\text{WALPHA})=\sum_{s=1}^{\text{LTRUE}+1} \text{WALPHA}(s)*d^{s-1} \quad ,$$

and

$$H(T,\text{WBETA})=\sum_{r=1}^{\text{LRBETA}} \text{WBETA}(r)*T^{r} \quad ;$$

(3) $$P(T,d)=1-\exp\{-g(d,\text{WALPHA})*[H(T,\text{WBETA})-\text{WBASE}(d)]\} \tag{5.7.9}$$

where

$$g(d,\text{WALPHA})=\sum_{s=1}^{\text{LTRUE}+1} \text{WALPHA}(s)\cdot d^{s-1} \quad ,$$

$$H(T,WBETA)= \sum_{r=1}^{LRBETA} WBETA(r)*T^{r} ,$$

and

WBASE(d) = WBASE(i) if d is the i-th smallest dose level;

(4) $$P(T,d)=1-\exp\{-g(d,WALPHA)*H[T,WBETA,WBASE(d)]\} \qquad (5.7.10)$$

where

$$g(d,WALPHA)= \sum_{s=1}^{LTRUE+1} WALPHA(s)*d^{s-1} ,$$

$$H[T,WBETA,WBASE(d)]= \sum_{r=1}^{LRBETA} WBETA(r)*[T-WBASE(d)]^{r} ,$$

and

WBASE(d) = WBASE(i) if d is the i-th smallest dose level;

(5) $$P(T,d)=1-\exp\{-\sum_{s=0}^{5} \sum_{r=1}^{5} WKAPPA(s,r)*d^{s}T^{r}\}; \text{ and} \qquad (5.7.11)$$

(6) $$P(T,d)=1-\exp\{-\sum_{s=0}^{5} \sum_{r=1}^{5} WKAPPA(s,r)*d^{s}*[T-WBASE(d)]^{r}\} \qquad (5.7.12)$$

where

WBASE(d) = WBASE(i) if d is the i-th smallest dose level.

Of course, the user must specify any of the following parameters which are a part of the form of P(T,d) selected by the user:

LTRUE, WALPHA(1), ..., WALPHA(LTRUE+1) ,

WBASE(1), ..., WBASE(D), LRBETA ,

WBETA(1), ..., WBETA(LRBETA) , TRUEK ,

WKAPPA(0,1), ..., WKAPPA(5,5) .

If the user wants to simulate a competing risk, the time of death, $\tau$, from this risk will be independent of the time to response, t, and have the following Weibull cumulative distribution function:

$$P(\tau \leq T) = 1 - \exp\{-ATAU*(T-W)^{KK}\} \qquad (5.7.13)$$

where ATAU, W, and KK are specified by the user. If the user does not want to simulate a competing risk, $\tau$ is set equal to $+\infty$.

The user may incorporate serial sacrifices into the simulation or have TSACR set equal to $+\infty$. If serial sacrifices are desired, the user must specify for each dose level, say $d_i$, (1) the number, NSACR(i), of distinct sacrifice times, (2) the sacrifice times TSACR(i,1), TSACR(i,2), ..., TSACR[i,NSACR(i)], and (3) the number NTSACR(i,j), of experimental units to be scheduled for sacrifice at TSACR(i,j), j = 1, ..., NSACR(i). The first NTSACR(i,1) experimental units at the i-th dose level are sacrificed at TSACR(i,1), the next NTSACR(i,2) experimental units are sacrificed at TSACR(i,2), and so forth until all experimental units at the i-th dose level in the group are accounted for.

The user must specify a value for TTERM which is the maximum time an experimental unit can be on experiment. If all experimental units are put on experiment at the same time, then TTERM would be the end of the experiment. If a lifetime study is to be simulated, a very large number should be specified for TTERM.

The user may want to simulate an experiment where on the average 100*PART % of the responses that occur are not detected until the time of death or sacrifice and on the average 100*(1.0-PART) % of the responses that occur are detected immediately.

Therefore, the user must specify a value for PART, $0 \leq \text{PART} \leq 1.0$. If PART = 0.0, then all responses are detected immediately; i.e., all responses correspond to observations Type 1, and there are no Type 2 observations. On the other hand, if PART = 1.0, then no responses are detected until time of death or sacrifice; i.e., all responses correspond to observations of Type 2, and there are no Type 1 observations.

The user may also request that the time scale be partitioned or not partitioned. If the time scale is not partitioned, each value for TOBS is left unchanged and treated individually. If the time scale is to be partitioned, then the user must specify the number, NTPART, of time partition points and their values TPART(1), ..., TPART(NTPART). The TPART's need not be equally spaced. If the time scale is partitioned, then each TOBS is rounded up to the smallest TPART(i) satisfying

$$\text{TOBS} \leq \text{TPART}(i) \ .$$

Any TOBS > TPART(NTPART) is rounded down to TPART(NTPART). Partitioning the time scale corresponds to rounding the observation times off to the day, week, month, etc. that they fell into. The restricted maximum likelihood estimation process can require much less time if the time scale is partitioned. This savings arises because the program need not consider each observation individually but only each TPART(i) and how many observations there were of each type - Type 1, Type 2, and Type 3. The user is cautioned to not use too coarse a time partition (NTPART too small) since this may distort the time to response information.

Finally, the user must specify a number IY, which will initialize the random number generator which is used in the simulation process. IY can be any 8 digit number. Since IY is specified by the user and also printed by MRS. T 1981, it is possible for the user to rerun an analysis on the same set of simulated data by using the same value for IY.

## 6. Specific Input Instructions for MRS. T 1981

The input to MRS. T 1981 is described below. The input will be described as though it were on computer cards but, of course, it could be on tape, etc. Each card input instruction will contain Card Order, Column, Format, Description.

The "Card Order" indicates the relative position of the card among all input cards. Some cards apply to only certain analyses and hence these cards are not always included. The circumstances under which a card is to be deleted are specified.

Since an input card often contains more than 1 piece of information, the "Column" indicates the specific column or columns where the particular information is to be placed. An input card has a maximum length of 80 columns (Columns 1 - 80).

The "Format" entry indicates the way in which the input information is to be positioned within its specified columns. For example, I1 means a one digit integer. An I5 means a 5 digit integer. All blanks are read as zeroes. All entries should be positioned within their specified columns so as to be right justified. Hence to read in the number 10 in I5 format the entry could be either 00010 or 3 blanks followed by 10. The number 1 in I2 format could be read in as 01 or one blank then 1. The number 0 in I2 format could be read in as 00 or two blanks. Also a format of F10.0 means a 10 digit decimal number. A decimal point should be included. If a decimal point is not included in the 10 columns, a decimal point is inserted after the tenth digit. For example 5.0 could be read in F10.0 format as 5.0 followed by seven blanks, seven blanks followed by 5.0, eight blanks followed by 5., nine blanks followed by 5, etc. A format of 2F10.0 calls for one 10 digit decimal number followed immediately by a second 10 digit decimal number. For example, 5.2 and 6. could be read in 2F10.0 format as 5.2 followed by seven blanks followed by 6. followed by eight blanks. Format 8F10.0 means up to eight consecutive 10 digit decimal numbers. If, for example, 20 decimal numbers were to be read in 8F10.0 format, then 8 ten digit decimal numbers would be on the first card, 8 ten digit decimal numbers on the second card, and 4 ten digit decimal numbers in the first 40 columns of the third card.

The "Description" indicates what information is to be provided for the specified "Card Order", "Column", and "Format". The description indicates the variable name assigned by the program to this information. Where possible the corresponding notation used in Section 5 is also included. An expository description is also often given as is any limitation on the acceptable values of the information. For example, the first card calls for the number of dose levels to be specified. N is the variable name assigned by the program to the number of dose levels. D is the notation used in Section 5 for the number of dose levels. $N \leq 10$ means that the current program will function correctly only if the specified number of dose levels is less than or equal to 10.

| Card Order | Column | Format | Description |
|---|---|---|---|
| A | 1-80 | Any | TITLE = any title or name for this run of the program. This title will be printed at the beginning of the output. |
| A.1 | 1 | I1 | IPRINT = 1 if the input is to be printed out as it is being read in. This option helps debug the input.<br>IPRINT = 0 if the input is not to be printed out as it is being read in. |
| B | 1-2 | I2 | N = number of dose levels; D.<br>$1 \leq N \leq 10$. |
| C | 1-80 | 8F10.0 | X(1), ..., X(N) = dose levels; $d_1, \ldots, d_D$<br>(Note X(1) must be 0.0 even if no observations are to be simulated or read in for this dose level. If no observations are simulated or read in for X(1) = 0.0, then a zero spontaneous rate is assumed; i.e., P(T,0) = 0 for all T.)<br>If $N > 8$, then two cards will be required with X(1), ..., X(8) on the first card and X(9), ..., X(N) on the second card beginning in Column 1. |

| | | | |
|---|---|---|---|
| D | 1-80 | 16I5 | L(1, I), I = 1, ..., N<br>= nonnegative number of observations at the I-th dose level (I = 1, ..., N) for each group.<br>(L(1, 1) may<br>= 0 if no observations are to be simulated or read in at the zero dose level.)<br>$0 \leq L(1, I) \leq 150$.<br>(If on Card YY IEXPD = 1 and on Card ZZ JREAD = 1, then the upper bound of 150 is not applicable and any value $\geq 0$ is allowable.) |
| E | 1-2 | I2 | NSGRP = number of additional groups of data to be simulated; G-1.<br>$0 \leq NSGRP \leq 9$ |

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Cards F - L describe the model which is to be fit to the observations.

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| | | | |
|---|---|---|---|
| F | 1 | I1 | NALPHA = the order of the polynomial estimator of $g(d; \alpha)$; a.<br>$1 \leq$ NALPHA $\leq 9$ |
| | 3 | I1 | INTA = 0 implies that an initial estimate of the $\alpha$ vector is to be read in.<br>INTA = 1 implies that an initial estimate of the $\alpha$ vector is to be computed by the program. |
| G | (Included only if INTA = 0 on Card F.) | | |
| G | 1-80 | 8F10.0 | AINT (1), ..., AINT (NALPHA + 1) corresponding to the initial estimates of $\alpha_0, \alpha_1, \ldots, \alpha_{NALPHA}$ respectively. |
| H | 1-2 | I2 | NBETA = the number, b, of terms in the estimator of $H(T;\beta) = \sum_{r=1}^{b} \beta_r \theta_r(T)$.<br>$1 \leq$ NBETA $\leq 10$ |
| | 4 | I1 | IHOPT = 1 if $\theta_r(T) = T^r$; so that $H(T;\beta)$ is estimated by a polynomial in T of order NBETA.<br>IHOPT = 2 if $\theta_r(T)$ is to be determined by the ITHETA vector to be read in |

| | | | |
|---|---|---|---|
| | 6 | I1 | INTB = 0 implies that the initial estimate of the β vector is to be read in.<br>INTB = 1 implies that an initial estimate of the β vector is to be computed by the program.<br>INTB = 2 implies that the estimate of the β vector is to be read in and kept fixed (not changed) during the estimation process. |
| I | (Included only if IHOPT = 2 on Card H.) | | |
| I | 1-50 | 10I5 | ITHETA (1), ..., ITHETA (NBETA)<br>ITHETA (r) = j implies<br>$\theta_r(T) = T^j$ if $1 \leq j \leq 10$<br>$= \ell n\ (T+1)$ if $j = 11$<br>$= e^T - 1$ if $j = 12$ |
| J | (Included only if INTB = 0 or 2 on Card H.) | | |
| J | 1-80 | 8F10.0 | BINT (1), ..., BINT (NBETA) corresponding to the initial estimates of $\beta_1, \beta_2, \ldots, \beta_{NBETA}$ respectively. |
| K | 1 | I1 | IDELTA = 1 implies that $H(T;\beta)$ will be generalized to $H(T;\beta)-\gamma(d)$<br>IDELTA = 2 implies that $H(T;\beta)$ will be generalized to $H[T-\phi(d);\beta]$.<br>Note that $\gamma(d)$ and $\phi(d)$ can not be both in the model at the simultaneously. |

| | | | |
|---|---|---|---|
| | 3 | I1 | INTDEL = 0 implies that an initial estimate of the DELTA vector (either $\gamma$ if IDELTA = 1 or $\phi$ if IDELTA = 2) is to be read in.<br>INTDEL = 1 implies the initial estimate of the DELTA vector is to be the zero vector.<br>INTDEL = 2 implies that the DELTA vector is to be read in and kept fixed (not changed) during the estimation process.<br>Note that INTDEL = 2 and reading in DINT = 0 together imply that both $\gamma(d)$ and $\phi(d)$ will be eliminated from the model. |
| L | (Included only if INTDEL = 0 or 2 on Card K.) | | |
| L | 1-80 | 8F10.0 | DINT (1), ..., DINT (N) corresponding to the initial estimates of the DELTA vector (either $\gamma[X(1)], \ldots, \gamma[X(N)]$ if IDELTA = 1 or $\phi[X(1)], \ldots, \phi[X(N)]$ if IDELTA = 2). |

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Cards M - O govern the description of the observations.

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|---|---|---|---|
| M | 1-5 | 5I1 | IDOBS (1), ..., IDOBS (5)<br>IDOBS (i) = 0 means Table A.i is *not* to be printed.<br>IDOBS (i) = 1 means Table A.i is to be printed. (IDOBS (4) is a special case.<br>IDOBS (1): Table A.1 showing the observations as they have been read in or simulated.<br>IDOBS (2): Table A.2 showing the observed number and percentage of observations by type and group.<br>Type 1 means a response occurred and was detected immediately<br>Type 2 means a response occurred and was not detected until death or sacrifice<br>Type 3 means no response occurred<br>IDOBS (3): Table A.3 showing the observed number and percentage of observations by type, group, and dose level. |

| | | | |
|---|---|---|---|
| | | | IDOBS (4): Table A.4 showing the observed proportion of responses by specified times T for each dose level and each group. |
| | | | IDOBS (4) = 1 means Table A.4 is printed only for the first group.<br>IDOBS (4) = 2 means Table A.4 is printed for each group separately. |
| | | | IDOBS (5): Table A.5 showing the minimum observation time at each dose level for each group. |
| N and O | (Included only if IDOBS (4) = 1 on Card M.) | | |
| N | 1-2 | I2 | NDTIME = the number of specified times T in Table A.4.<br>$1 \le \text{NDTIME} \le 40$ |
| O | 1-80 | 8F10.0 | DTIME (1), ..., DTIME (NDTIME) corresponding to the time T desired in Table A.4.<br>$0.0 < \text{DTIME} (\cdot)$ |

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Cards P - T govern the description of the fitted model and the estimation process.

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

| | | | |
|---|---|---|---|
| P | 1-4 | 4I1 | IDEST (1), ..., IDEST (4)<br>IDEST (i) = 0 means Table B.i is not to be printed.<br>IDEST (i) = 1 means Table B.i is to be printed only for the first group.<br>IDEST (i) = 2 means Table B.i is to printed for each group separately.<br><br>IDEST (1): Table B.1 showing the simplest characterization of the observed and predicted proportions of responses by time T at dose level d for specified times T and all experimental dose levels d.<br>IDEST (2): Table B.2 showing an approximate chi-squared goodness-of-fit test on the simplest characterization of the observed and predicted proportions of responses by time T at dose level d for specified times T and all experimental dose levels d. |

| | | | |
|---|---|---|---|
| | | | IDEST (3): Table B.3 showing the second characterization (using estimated conditional probabilities) of the observed and predicted proportions of responses by time T at dose level d for specified times T and all experimental dose levels d.<br>IDEST (4): Table B.4 showing an approximate chi-squared goodness-of-fit test on the second characterization (using estimated conditional probabilities) of the observed and predicted proportions of responses by time T at dose level d for specified times T and all experimental dose levels d. |
| Q and R | (Included only if IDEST (1) = 1 or IDEST (3) = 1 or both on Card P.) | | |
| Q | 1-2 | I2 | NCTIME = the number of specified times T in Tables B.1 and B.3<br>$1 \le \text{NCTIME} \le 40$. |
| R | 1-80 | 8F10.0 | CTIME (1), ..., CTIME (NCTIME) corresponding to the times T desired in Tables B.1 and B.3. |

S and T (Included only if IDEST (2)= 1 or IDEST (4) = 1 or both on Card P.)

| | | | |
|---|---|---|---|
| S | 1-2 | I2 | NXTIME = the number of specified times T in Tables B.2 and B.4. $1 \leq \text{NXTIME} \leq 40$. |
| T | 1-80 | 8F10.0 | XTIME (1), ..., XTIME (NXTIME) corresponding to the times T desired in Tables B.2 and B.4. |

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Cards U - DD govern the description of some implications of the fitted model.

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

| | | | |
|---|---|---|---|
| U | 1-3 | 3I1 | IDIMP (1), ..., IDIMP (3)<br>IDIMP (i) = 0 means Table C.i is *not* to be printed.<br>IDIMP (i) = 1 means Table C.i is to be printed only for the first group.<br>IDIMP (i) = 2 means Table C.i is to be printed for each group separately.<br>IDIMP (1): Table C.1 showing the estimated probability of a response at specified times T and specified doses d.<br>IDIMP (2): Table C.2 showing the estimated time T to reach a specified probability of a response for a specified dose d.<br>IDIMP (3): Table C.3 showing the estimated mean free response period at specified doses for each specified maximum period. |

| | | | |
|---|---|---|---|
| V, W, and X | (Included only if IDIMP (1) = 1 on Card U.) | | |
| V | 1-2 | I2 | NTABS = the number of equally spaced intermediate times T between the minimum time TABMIN in Table C.1 and the maximum time TABMAX in Table C.1.<br>A total of NTABS + 2 times T will be considered in Table C.1<br>$0 \le \mathrm{NTABS} \le 40$ |
| | 11-20 | F10.0 | TABMIN |
| | 21-30 | F10.0 | TABMAX |
| W | 1-2 | I2 | NXS = the number of specified doses d to be considered in Table C.1.<br>$1 \le \mathrm{NXS} \le 10$ |
| X | 1-80 | 8F10.0 | XS (1), ..., XS (NXS) corresponding to the desired doses d in Table C.1. |
| Y - AA | (Included only if IDIMP (2) = 1 on Card U.) | | |
| Y | 1-2 | I2 | NRISKD = the number of dose levels desired in Table C.2.<br>$1 \le \mathrm{NRISKD} \le 50$ |
| | 4-5 | I2 | NRISKL = the number of risk levels (probabilities of a response) desired in Table C.2.<br>$1 \le \mathrm{NRISKL} \le 10$ |
| Z | 1-80 | 8F10.0 | RISKD (1), ..., RISKD (NRISKD) corresponding to the dose levels desired in Table C.2.<br>$0 \le \mathrm{RISKD}\ (\cdot)$ |

| | | | |
|---|---|---|---|
| AA | 1-80 | 8F10.0 | RISKL (1), ..., RISKL (NRISKL) corresponding to the risk levels desired in Table C.2.<br>$0.0 < \text{RISKL}(\cdot) < 1.0$ |
| BB - DD | (Included only if IDIMP (3) = 1 on Card U.) | | |
| BB | 1-2 | I2 | NDMFP = number of dose levels for which the mean free periods are to be calculated for Table C.3.<br>$1 \leq \text{NDMFP} \leq 50$ |
| | 4 | I1 | NMAXP = number of maximum periods, t*, desired for Table C.3.<br>$1 \leq \text{NMAXP} \leq 5$ |
| CC | 1-80 | 8F10.0 | DMFP (1), ..., DMFP (NDMFP) corresponding to the dose levels desired for Table C.3.<br>$0.0 \leq \text{DMFP}(\cdot)$ |
| DD | 1-50 | 5F10.0 | TMFP (1), ..., TMFP (NMAXP) corresponding to the maximum periods desired for Table C.3.<br>$0 < \text{TMFP}(\cdot)$ |

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Cards EE - SS govern the description of the estimated "acceptable" dose levels and their confidence limits.

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

| | | | |
|---|---|---|---|
| EE | 1 | I1 | IDVSD = 0 implies that the virtually safe dose is not to be considered.<br>IDVSD = 1 implies that the virtually safe dose is to be considered. |
| FF - II | (Included only if IDVSD = 1 on Card EE.) | | |
| FF | 1-5 | 5I1 | IDVSDT (1), ..., IDVSDT (5)<br>IDVSDT (i) = 0 implies Table VSD.i is not to be printed.<br>IDVSDT (i) $\geq$ 1 implies that Table VSD.i is to be printed for the first group. = 1 is the standard printing. > 1 implies a modified printing.<br>IDVSDT (1) = 1: the estimated virtually safe dose corresponding to the first group.<br>IDVSDT (1) = 2: the estimated virtually safe dose will be printed for each group separately.<br>IDVSDT (2) = 1: the estimated 90% lower confidence limit on the virtually safe dose. |

IDVSDT (2) = 2: the estimated 95% lower confidence limit on the virtually safe dose.

IDVSDT (2) = 3: the estimated 99% lower confidence limit on the virtually safe dose.

IDVSDT (3) = 1: the ratio of the estimated virtually safe dose from the first group to the lower confidence limit on the virtually safe dose.

IDVSDT (4) = 1: (if the data has been simulated) the ratio of the estimated virtually safe dose from the first group to the true virtually safe dose.

IDVSDT (5) = 1: (if the data has been simulated) the ratio of the lower confidence limit on the virtually safe dose to the true virtually safe dose.

| | | | |
|---|---|---|---|
| GG | 1 | I1 | NTSTAR = the number of times T* to be considered in the definition of a virtually safe dose.<br>$1 \le \text{NTSTAR} \le 5$ . |
| | 3 | I1 | NPINC = the number of permissible increments $\pi$ to be considered in the definition of a virtually safe dose.<br>$1 \le \text{NPINC} \le 5$ . |

| | | | |
|---|---|---|---|
| HH | 1-50 | 5F10.0 | TSTAR (1), ..., TSTAR (NTSTAR) corresponding to the times T* to be considered in defining the virtually safe dose. |
| II | 1-50 | 5F10.0 | PINC (1), ..., PINC (NPINC) corresponding to the permissible increments π to be considered in defining the virtually safe dose. For example, PINC = .0001 is the permissible increment corresponding to an increment of $10^{-4}$ in the spontaneous response free rate. |
| JJ | 1 | I1 | IDLRD<br>IDLRD = 0 implies that the late risk dose is not to be considered.<br>IDLRD = 1 implies that the late risk dose is to be considered. |
| KK - NN | (Included only if IDLRD = 1 on Card JJ.) | | |
| KK | 1-5 | 5I1 | IDLRDT (1), ..., IDLRDT (5)<br>IDLRDT (i) = 0 implies Table LRD.i is not to be printed.<br>IDLRDT (i) $\geq$ 1 implies that Table LRD.i is to be printed for the first group.<br>= 1 is the standard printing.<br>> implies a modified printing. |

IDLRDT (1) = 1: the estimated late risk dose corresponding to the first group.

IDLRDT (1) = 2: the estimated late risk dose will be printed for each group separately.

IDLRDT (2) = 1: the estimated 90% lower confidence limit on the late risk dose.

IDLRDT (2) = 2: the estimated 95% lower confidence limit on the late risk dose.

IDLRDT (2) = 3: the estimated 99% lower confidence limit on the late risk dose.

IDLRDT (3) = 1: the ratio of the estimated late risk dose from the first group to the lower confidence limit on the late risk dose.

IDLRDT (4) = 1: (if the data has been simulated) the ratio of the estimated late risk dose from the first group to the true late risk dose.

IDLRDT (5) = 1: (if the data has been simulated) the ratio of the lower confidence limit on the late risk dose to the true late risk dose.

| | | | |
|---|---|---|---|
| LL | 1-2 | I2 | NLATET = the number of times t** to be used in defining the late risk dose.<br>$1 \leq NLATET \leq 50$. |
| | 4-5 | I2 | NLATEF = the number of fractions f to be used in defining the late risk dose.<br>$1 \leq NLATEF \leq 10$. |
| MM | 1-80 | 8F10.0 | RLATET (1), ..., RLATET (NLATET) corresponding to the times t** to be used in defining the late risk dose. |
| NN | 1-80 | 8F10.0 | RLATEF (1), ..., RLATEF (NLATEF) corresponding to the proportions f to be used in defining the late risk dose.<br>$0 < RLATEF < 1.0$.<br>Presumably RLATEF should be near 1.0. |
| OO | 1 | I1 | IDMFD<br>IDMFD = 0 implies that the mean free dose is not to be considered.<br>IDMFD = 1 implies that the mean free dose is to be considered. |
| PP - SS | (Included only if IDMFD = 1 on Card OO.) | | |
| PP | 1-5 | 5I1 | IDMFDT (1), ..., IDMFDT (5)<br>IDMFDT (i) = 0 implies Table MFD.i is not to be printed. |

IDMFDT (i) $\geq$ 1 implies that Table MFD.i is to be printed for the first group. = 1 is the standard printing. > 1 implies a modified printing.

IDMFDT (1) = 1: the estimated mean free dose corresponding to the first group.

IDMFDT (1) = 2: the estimated mean free dose will be printed for each group separately.

IDMFDT (2) = 1: the estimated 90% lower confidence limit on the mean free dose.

IDMFDT (2) = 2: the estimated 95% lower confidence limit on the mean free dose.

IDMFDT (2) = 3: the estimated 99% lower confidence limit on the mean free dose.

IDMFDT (3) = 1: the ratio of the estimated mean free dose from the first group to the lower confidence limit on the mean free dose.

| | | | |
|---|---|---|---|
| | | | IDMFDT (4) = 1: (if the data has been simulated) the ratio of the estimated mean free dose from the first group to the true mean free dose.<br>IDMFDT (5) = 1: (if the data has been simulated) the ratio of the lower confidence limit on the mean free dose to the true mean free dose. |
| QQ | 1-2 | I2 | NMFDMP = the number of maximum periods t*** used in defining the mean free dose.<br>$1 \leq$ NMFDMP $\leq 50$. |
| | 4-5 | I2 | NMFDP = the number of proportions $\varepsilon$ used in defining the mean free dose.<br>$1 \leq$ NMFDP $\leq 10$. |
| RR | 1-80 | 8.F10.0 | RMFDMP (1), ..., RMFDMP (NMFDMP) corresponding to the maximum periods t*** to be used in defining the mean free dose. |
| SS | 1-80 | 8F10.0 | RMFDP (1), ..., RMFDP (NMFDP) corresponding to the proportions $\varepsilon$ used in defining the mean free dose. |

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Cards TT - XX govern the estimation of the model parameters.

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

| | | | |
|---|---|---|---|
| TT | 1 | I1 | IMLE<br>IMLE = 0 implies that the model parameters have already been estimated and are to be read in.<br>IMLE = 1 implies that the model parameters are to be estimated using maximum likelihood estimation. |

UU - WW (Included only if IMLE = 0 on Card TT.)

(Cards UU, VV, and WW are read in for group 1, then cards UU, VV, and WW are read in for group 2, ..., then cards UU, VV, WW are read in for the NGRP-th group.)

| | | | |
|---|---|---|---|
| UU | 1-80 | 8F10.0 | ALPHAS (K, 1), ..., ALPHAS (K,NALPHA + 1) corresponding to the estimates of $\alpha_0$, $\alpha_1$, ..., $\alpha_{NALPHA}$ for the K-th group. |
| VV | 1-80 | 8F10.0 | BETAS (K, 1), ..., BETAS (K,NBETA) corresponding to the estimates of $\beta_1$, ..., $\beta_{NBETA}$ for the K-th group. |
| WW | 1-80 | 8F10.0 | DELTAS (K, 1), ..., DELTAS (K,N) corresponding to the estimates of either $\gamma_1$, ..., $\gamma_N$ or $\phi_1$, ..., $\phi_N$ for the K-th group. |

| | | | |
|---|---|---|---|
| XX | (Included only if IMLE = 1 on Card TT.) | | |
| XX | 1 | I1 | IMONO<br>IMONO = 0 if the estimated dose function $g(d;\hat{\alpha})$ is required to be nonnegative but not necessarily monotone nondecreasing in the dose level d.<br>IMONO = 1 if $g(d;\hat{\alpha})$ is required to be both nonnegative and monotone nondecreasing in the dose level d. |

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Cards YY - ZZZ govern the data that is to be considered by the program.

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

| | | | |
|---|---|---|---|
| YY | 1 | I1 | IEXPD<br>IEXPD = 0 if the data is to be simulated by the program as opposed to experimental data to be read in.<br>IEXPD = 1 if the data is experimental data to be read in as opposed to data to be simulated by the program. |

ZZ - CCC (Included only if IEXPD = 1 on Card YY.)

| | | | |
|---|---|---|---|
| ZZ | 1 | I1 | JREAD<br>JREAD = 0 if each observation is to be read in separately.<br>JREAD = 1 implies that several observations have been made at the same time and a more efficient input format is to be used. |

AAA - BBB (Included only if IEXPD = 1 on Card YY and JREAD = 1 on Card ZZ.)

Read in the cards AAA and BBB in the following order:

| | |
|---|---|
| AAA<br>BBB's | Group 1<br>0 dose level |
| AAA<br>BBB's | Group 1<br>Smallest positive dose level |

⋮

| | |
|---|---|
| AAA | Group 1 |
| BBB's | Largest dose level |

END OF PROGRAM INPUT (if JREAD = 1 and IEXPD = 1).

(Omit the cards for the I-th dose level if there were no observations at the I-th dose level; i.e., L(1,I) = 0 on Card E.)

| | | | |
|---|---|---|---|
| AAA | 1-5 | I5 | NTIME (1,I) = the number of different observation times for the 1-th group and the I-th dose level.<br>$1 \leq \text{NTIME} \leq 40$. |
| BBB | (NTIME (1,I) cards; i.e., J = 1, 2, ..., NTIME (1,I) below) | | |
| BBB | 1-5 | I5 | NRT (1,I,J,1) = number of observations of type 1 at the J-th time, RTIME (1,I,J), at the I-th dose level for the 1-th group - observations of type 1 are where a response has occurred and was detected immediately; that is, the time when the response occurred is known. |
| | 6-10 | I5 | NRT (1,I,J,2) = number of observations of type 2 at the J-th time, RTIME (1,I,J), at the I-th dose level for the 1-th group - observations of type 2 are where a response has occurred by the J-th time, RTIME (1,I,J), but the exact time of occurrence is unknown. |

| | | |
|---|---|---|
| 11-15 | I5 | NRT (1,I,J,3) = number of observations of type 3 at the J-th time, RTIME (1,I,J), at the I-th dose level for the 1-th group - observations of type 3 are where a response has not occurred by the J-th time, RTIME (1,I,J). |
| 16-25 | F10.0 | RTIME (1,I,J) = the J-th observation time at the I-th dose level for the 1-th group.<br>RTIME (1,I,J) > 0. |

EXAMPLE of input for IEXPD = 1 and JREAD = 1 when there is 3 dose levels (I = 1,2,3), and the following number of times [NTIME (1,I), with J = 1, ..., NTIME (1,I)]

<u>NTIME (1,I)</u>

NTIME (1,1) = 2

NTIME (1,2) = 2

NTIME (1,3) = 3

```
2                                AAA:  I=1
0      0       5        10.0     BBB:  I=1, J=1
1      1       8        20.0     BBB:  I=1, J=2
2                                AAA:  I=2
1      0      19        12.0     BBB:  I=2, J=1
0     10      15        18.5     BBB:  I=2, J=2
3                                AAA:  I=3
0      1       4        10.0     BBB:  I=3, J=1
0      1       0        15.0     BBB:  I=3, J=2
0      2       7        20.0     BBB:  I=3, J=3
```

CCC (Included only if IEXPD = 1 on Card YY and JREAD = 0 on Card ZZ.)

If IEXPD = 1 and JREAD = 0, then each observation is read in separately in the following order:

L(1,1) cards for group 1 and the zero dose level

L(1,2) cards for group 1 and the smallest positive dose level

⋮

L(1,N) cards for group 1 and the largest dose level

END OF PROGRAM INPUT (if IEXPD = 1 and JREAD = 0).

(Omit the cards for the I-th dose level if there were no observations at the I-th dose level; i.e., L(1,I) = 0 on Card E.)

| | | | |
|---|---|---|---|
| CCC | 1 | I1 | IT (1,J,I)<br>IT (1,J,I) = 1 if the J-th observation at the I-th dose level for the 1-th group is of type 1 - observations of type 1 are where a response has occurred and was detected immediately; that is, the time when the response occurred is OBS (1,J,I).<br>IT (1,J,I) = 2 if the J-th observation at the I-th dose level for the 1-th group is of type 2 - observations of type 2 are where a response has occurred by OBS (1,J,I) but the exact time of occurrence is unknown.<br>IT (1,J,I) = 3 if the J-th observation at the I-th dose level for the 1-th group is of type 3 - observations of type 3 are where a response has not occurred by OBS (1,J,I). |
| | 2-11 | F10.0 | OBS (1,J,I) = J-th observation time at the I-th dose level for the 1-th group.<br>OBS (1,J,I) > 0. |

DDD - ZZZ (Included only if IEXPD = 0 on Card YY; that is, included only if the data is to be simulated.)

DDD 1 I1 IHAZRD implies the form of the simulated probability, P(T,d), of a response by time T at dose d.

IHAZRD = 1 if the hazard rate has the weibull form

$$P(T,d) = 1.0 - \exp\{-g(d,WALPHA)*H[T,TRUEK,WBASE(d)]\}$$

where

$$g(d,WALPHA)= \sum_{s=1}^{LTRUE+1} WALPHA(s)*d^{s-1},$$

$$H[T,TRUEK,WBASE(d)]=[T-WBASE(d)]^{TRUEK},$$

and

WBASE(d)=WBASE(i) if d is the i-th smallest dose level.

IHAZRD = 2 if the hazard rate has the simple product form

$$P(T,d) = 1 - \exp\{-g(d,WALPHA)*H(T,WBETA)\}$$

where

$$g(d,WALPHA)= \sum_{s=1}^{LTRUE+1} WALPHA(s)*d^{s-1},$$

and

$$H(T,WBETA)= \sum_{r=1}^{LRBETA} WBETA(r)*T^{r} .$$

IHAZRD = 3 if the hazard rate has the form

$$P(T,d) = 1 - \exp\{-g(d,WALPHA)*[H(T,WBETA)-WBASE(d)]\}$$

where

$$g(d,WALPHA)= \sum_{s=1}^{LTRUE+1} WALPHA(s)*d^{s-1},$$

$$H(T,WBETA)= \sum_{r=1}^{LRBETA} WBETA(r)*T^{r} ,$$

and

WBASE(d) = WBASE(i) if d is the i-th smallest dose level.

IHAZRD = 4 if the hazard rate has the form

$$P(T,d) = 1 - \exp \{-g(d,WALPHA)* H[T,WBETA,WBASE(d)]\}$$

where

$$g(d,WALPHA)= \sum_{s=1}^{LTRUE+1} WALPHA(s)*d^{s-1},$$

$$H[T,WBETA,WBASE(d)]= \sum_{r=1}^{LRBETA} WBETA(r)* [T-WBASE(d)]^{r} ,$$

and

WBASE(d) = WBASE(i) if d is the i-th smallest dose level.

IHAZRD = 5 if the hazard rate has the general polynomial form

$$P(T,d) = 1 - \exp \{- \sum_{s=0}^{5} \sum_{r=1}^{5} WKAPPA (s,r)*d^{s}T^{r}\}.$$

IHAZRD = 6 if the hazard rate has the form

$$P(T,d) = 1 - \exp \{- \sum_{s=0}^{5} \sum_{r=1}^{5} WKAPPA (s,r)*d^{s}*[T-WBASE(d)]^{r}\}$$

| | | |
|---|---|---|
| | | where<br>$WBASE(d) = WBASE(i)$ if d is the i-th smallest dose level. |
| 2 | I1 | ICRISK<br>ICRISK = 0 if there is no competing risk.<br>ICRISK = 1 if there is a competing risk in which case the time of death from this risk has a cumulative distribution function of the form<br>$P(\text{death time} \le T) = 1 - \exp\{-ATAU*(T-W)^{KK}\}$. |
| 3 | I1 | ITSACR<br>ITSACR = 0 if no serial sacrifice times are to be specified.<br>ITSACR = 1 if serial sacrifice times are to be specified. |
| 4 | I1 | JPART<br>JPART = 0 if the time scale is not to be partitioned.<br>JPART = 1 if the time scale is to be partitioned in which case NTPART times ($TPART(1) \le \ldots \le TPART(NTPART)$) will be specified and each observation time, say T, will be rounded up to the smallest TPART(i) and that $T \le TPART(i)$. |

Cards EEE - QQQ refer to the parameters that need to be specified in the simulated hazard rate. These parameters are defined in the discussion of IHAZRD on card DDD.

| | | | |
|---|---|---|---|
| EEE and FFF | (Included only if IHAZRD $\leq$ 4 on card DDD.) | | |
| EEE | 1 | I1 | LTRUE. |
| | | | $0 \leq$ LTRUE $\leq 9$. |
| FFF | 1-80 | 8F10.0 | WALPHA(1), ..., WALPHA(LTRUE+1). |
| GGG | (Included only if IHAZRD = 1 on card DDD.) | | |
| GGG | 1-80 | 8F10.0 | WBASE(1), ..., WBASE(N), TRUEK. |
| HHH and III | (Included only if IHAZRD = 2, 3, or 4 on card DDD.) | | |
| HHH | 1-2 | I2 | LRBETA. |
| | | | $1 \leq$ LRBETA $\leq 10$. |
| III | 1-80 | 8F10.0 | WBETA(1), ..., WBETA(LRBETA). |
| JJJ | (Included only if IHAZRD = 3 or 4 on card DDD.) | | |
| JJJ | 1-80 | 8F10.0 | WBASE(1), ..., WBASE(N). |
| KKK - PPP | (Included only if IHAZRD = 5 or 6 on card DDD.) | | |
| KKK | 1-50 | 5F10.0 | WKAPPA(0,1), ..., WKAPPA(0,5). |
| LLL | 1-50 | 5F10.0 | WKAPPA(1,1), ..., WKAPPA(1,5). |
| MMM | 1-50 | 5F10.0 | WKAPPA(2,1), ..., WKAPPA(2,5). |
| NNN | 1-50 | 5F10.0 | WKAPPA(3,1), ..., WKAPPA(3,5). |
| OOO | 1-50 | 5F10.0 | WKAPPA(4,1), ..., WKAPPA(4,5). |
| PPP | 1-50 | 5F10.0 | WKAPPA(5,1), ..., WKAPPA(5,5). |
| QQQ | (Included only if IHAZRD = 6 on card DDD.) | | |
| QQQ | 1-80 | 8F10.0 | WBASE(1), ..., WBASE(N). |

| | | | |
|---|---|---|---|
| RRR | (Included only if ICRISK = 1 on card DDD.) | | |
| RRR | 1-10 | F10.0 | ATAU. |
| | 11-20 | F10.0 | KK. |
| | 21-30 | F10.0 | W. |
| SSS | 1-10 | F10.0 | PART<br>100*PART % of the observations which have a response before time of death or sacrifice will be of type 2, that is, the response will not be detected immediately but will be detected only at the time of death or sacrifice.<br>$0 \leq PART \leq 1.0$<br>(of course, PART = 0.0 implies that all responses will be detected immediately (type 1), and PART = 1.0 implies that all responses will not be detected until time of death or sacrifice.) |
| TTT | 1-10 | F10.0 | TTERM<br>The end of the simulation experiment is at time TTERM. Any experimental unit which has not developed a response by time TTERM becomes a type 3 observation (no response).<br>$0 < TTERM$. |

| | | | |
|---|---|---|---|
| UUU - WWW | | | (Included only if ITSACR = 1 on card DDD.) |
| UUU | 1-50 | 10I5 | NSACR(1), ..., NSACR(N).<br>NSACR (i) = number of serial sacrifice times at the i-th dose level for each group.<br>$0 \leq NSACR \leq 40$ |
| VVV | 1-50 | 10F5.0 | TSACR (i,1), ..., TSACR[i,NSACR(i)]. These are the sacrifice times for the i-th dose level.<br>One set of cards for each dose level, i = 1, ..., N, with NSACR(i) > 0. |
| WWW | 1-80 | 16I5 | NTSACR (i,1), ..., NTSACR[i,NSACR(i)]. At the i-th dose level NTSACR (i,1) experimental units will be sacrificed at time TSACR (i,1), NTSACR (i,2) experimental units will be sacrificed at time TSACR (i,2), etc.<br>One set of cards for each dose level, i = 1, ..., N, with NSACR (i) > 0.<br>$NTSACR \geq 1$. |
| XXX - YYY | | | (Included only if JPART = 1 on card DDD.) |
| XXX | 1-2 | I2 | NTPART = the number of possible observation times on the partitioned time scale.<br>$1 \leq NTPART \leq 40$ |

| | | | |
|---|---|---|---|
| YYY | 1-80 | 8F10.0 | TPART (1), ..., TPART (NTPART).<br>If the observation time is t and JPART = 1, then t is rounded to the following:<br>TPART (1) if $t \le$ TPART (1);<br>TPART (2) if TPART (1) $< t \le$ TPART (2);<br>etc.<br>TPART(NTPART-1) if TPART(NTPART-2) $< t \le$ TPART(NTPART-1);<br>TPART(NTPART) if $t >$ TPART(NTPART-1). |
| ZZZ | 1-8 | | IY = the initialization parameter for the simulation procedure.<br>IY can be any eight digit hexadecimal constant such that IY $\ge$ 10,000.<br>Examples:<br>IY = 123ABC77,<br>IY = 94756291,<br>IY = 15610001,<br>IY = 5151EE81,<br>IY = 05ED3CE1 . |

## References

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## Appendix A

### Summary of MRS. T 1981 Input

In this summary only the "Card Order", "Column", "Format" and variable name or names assigned to the information on that card are listed. A detailed description of this information is given in Section 6.

| Card Order | Column | Formation | Information |
|---|---|---|---|
| A | 1-80 | Any | Title |
| A.1 | 1 | I1 | IPRINT |
| B | 1-2 | I2 | N |
| C | 1-80 | 8F10.0 | X(1), ..., X(N) |
| D | 1-80 | 16I5 | L(1,I)'s |
| E | 1-2 | I2 | NSGRP |

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Cards F - L describe the model which is to be fit to the observations.

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

| Card Order | Column | Formation | Information |
|---|---|---|---|
| F | 1 | I1 | NALPHA |
|  | 3 | I1 | INTA |
| G | (Included only if INTA = 0.) |  |  |
| G | 1-80 | 8F10.0 | AINT(1), ..., AINT(NALPHA+1) |
| H | 1-2 | I2 | NBETA |
|  | 4 | I1 | IHOPT |
|  | 6 | I1 | INTB |
| I | (Included only if IHOPT = 2.) |  |  |
| I | 1-50 | 10I5 | ITHETA(1), ..., ITHETA(NBETA) |
| J | (Included only if INTB = 0 or 2.) |  |  |
| J | 1-80 | 8F10.0 | BINT(1), ..., BINT(NBETA) |
| K | 1 | I1 | IDELTA |
|  | 3 | I1 | INTDEL |
| L | (Included only if INTDEL = 0 or 2.) |  |  |
| L | 1-80 | 8F10.0 | DINT(1),..., DINT(N) |

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Cards M - O govern the description of the observations.

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| | | | |
|---|---|---|---|
| M | 1-5 | 5I1 | IDOBS(1), ..., IDOBS(5) |
| N and Q | (Included only if IDOBS(4) ≥ 1.) | | |
| N | 1-2 | I2 | NDTIME |
| O | 1-80 | 8F10.0 | DTIME(1), ..., DTIME(NDTIME) |

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Cards P - T govern the description of the fitted model and the estimation process.

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

| | | | |
|---|---|---|---|
| P | 1-4 | 4I1 | IDEST(1), ..., IDEST (4) |
| Q and R | (Included only if IDEST (1) ≥ 1 and/or IDEST (3) ≥ 1.) | | |
| Q | 1-2 | I2 | NCTIME |
| R | 1-80 | 8F10.0 | CTIME(1), ..., CTIME(NCTIME) |
| S and T | (Included only if IDEST (2) ≥ 1 and/or IDEST (4) ≥ 1.) | | |
| S | 1-2 | I2 | NXTIME |
| T | 1-80 | 8F10.0 | XTIME(1), ..., XTIME(NXTIME) |

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Cards U - DD govern the description of some implications of the fitted model.

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

| | | | |
|---|---|---|---|
| U | 1-3 | 3I1 | IDIMP(1), ..., IDIMP(3) |
| V - X | (Included only if IDIMP(1) ≥ 1.) | | |
| V | 1-2 | I2 | NTABS |
| | 11-20 | F10.0 | TABMIN |
| | 21-30 | F10.0 | TABMAX |
| W | 1-2 | I2 | NXS |
| X | 1-80 | 8F10.0 | XS(1), ..., XS(NXS) |
| Y - AA | (Included only if IDIMP(2) ≥ 1.) | | |
| Y | 1-2 | I2 | NRISKD |
| | 4-5 | I2 | NRISKL |
| Z | 1-80 | 8F10.0 | RISKD(1), ..., RISKD(NRISKD) |
| AA | 1-80 | 8F10.0 | RISKL(1), ..., RISKL(NRISKL) |
| BB - DD | (Included only if IDIMP(3) ≥ 1.) | | |
| BB | 1-2 | I2 | NDMFP |
| | 4 | I1 | NMAXP |
| CC | 1-80 | 8F10.0 | DMFP(1), ..., DMFP(NDMFP) |
| DD | 1-50 | 5F10.0 | TMFP(1), ..., TMFP(NMAXP) |

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Cards EE - SS govern the description of the estimated "acceptable" dose levels and their confidence limits.

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| | | | |
|---|---|---|---|
| EE | 1 | I1 | IDVSD |
| FF - II | (Included only if IDVSD = 1.) | | |
| FF | 1-5 | 5I1 | IDVSD(1), ..., IDVSD(5) |
| GG | 1 | I1 | NTSTAR |
| | 3 | I1 | NPINC |
| HH | 1-50 | 5F10.0 | TSTAR(1), ..., TSTAR(NTSTAR) |
| II | 1-50 | 5F10.0 | PINC(1), ..., PINC(NPINC) |
| JJ | 1 | I1 | IDLRD |
| KK - NN | (Included only if IDLRD = 1.) | | |
| KK | 1-5 | 5I1 | IDLRDT(1),..., IDLRDT(5) |
| LL | 1-2 | I2 | NLATET |
| | 4-5 | I2 | NLATEF |
| MM | 1-80 | 8F10.0 | RLATET(1), ..., RLATET(NLATET) |
| NN | 1-80 | 8F10.0 | RLATEF(1), ..., RLATEF(NLATEF) |
| OO | 1 | I1 | IDMFD |
| PP - SS | (Included only if IDMFD = 1.) | | |
| PP | 1-5 | 5I1 | IDMFDT(1), ..., IDMFDT(5) |
| QQ | 1-2 | I2 | NMFDMP |
| | 4-5 | I2 | NMFDP |
| RR | 1-80 | 8F10.0 | RMFDMP(1), ..., RMFDMP(NMFDMP) |
| SS | 1-80 | 8F10.0 | RMFDP(1), ..., RMFDP(NMFDP) |

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Cards TT - XX govern the estimation of the model parameters.

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| | | | |
|---|---|---|---|
| TT | 1 | I1 | IMLE |
| UU - WW | (Included only if IMLE = 0.) | | |
| UU | 1-80 | 8F10.0 | ALPHAS(K,1), ..., ALPHAS(K,NALPHA+1) |
| VV | 1-80 | 8F10.0 | BETAS(K,1), ..., BETAS(K,NBETA) |
| WW | 1-80 | 8F10.0 | DELTAS(K,1), ..., DELTAS(K,N) |
| XX | 1 | I1 | IMONO |

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Cards YY - ZZZ govern the data that is to be considered by the program

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

| | | | |
|---|---|---|---|
| YY | 1 | I1 | IEXPD |
| ZZ - CCC | (Included only if IEXPD = 1.) | | |
| ZZ | 1 | I1 | JREAD |
| AAA - BBB | (Included only if IEXPD = 1 and JREAD = 1.) | | |
| AAA | 1-5 | I5 | NTIME(1,I) |
| BBB | 1-5 | I5 | NRT(1,I,J,1) |
| | 6-10 | I5 | NRT(1,I,J,2) |
| | 11-15 | I5 | NRT(1,I,J,3) |
| | 16-25 | F10.0 | RTIME(1,I,J) |
| CCC | (Included only if IEXPD = 1 and JREAD = 0.) | | |
| CCC | 1 | I1 | IT(1,J,I) |
| | 2-11 | F10.0 | OBS(1,J,I) |
| DDD - ZZZ | (Included only if IEXPD = 0.) | | |
| DDD | 1 | I1 | IHAZRD |
| | 2 | I1 | ICRISK |
| | 3 | I1 | ITSACR |
| | 4 | I1 | JPART |
| EEE and FFF | (Included only if IHAZRD ≤ 4.) | | |
| EEE | 1 | I1 | LTRUE |
| FFF | 1-80 | 8F10.0 | WALPHA(1), ..., WALPHA(LTRUE+1) |
| GGG | (Included only if IHAZRD = 1.) | | |
| GGG | 1-80 | 8F10.0 | WBASE(1), ..., WBASE(N), TRUEK |
| HHH - III | (Included only if IHAZRD = 2, 3, or 4.) | | |
| HHH | 1-2 | I2 | LRBETA |
| III | 1-80 | 8F10.0 | WBETA(1), ..., WBETA(LRBETA) |
| JJJ | (Included only if IHAZRD = 3 or 4.) | | |
| JJJ | 1-80 | 8F10.0 | WBASE(1), ..., WBASE(N) |
| KKK - PPP | (Included only if IHAZRD = 5 or 6.) | | |
| KKK | 1-50 | 5F10.0 | WKAPPA(0,1), ..., WKAPPA(0,5) |
| LLL | 1-50 | 5F10.0 | WKAPPA(1,1), ..., WKAPPA(1,5) |
| MMM | 1-50 | 5F10.0 | WKAPPA(2,1), ..., WKAPPA(2,5) |
| NNN | 1-50 | 5F10.0 | WKAPPA(3,1), ..., WKAPPA(3,5) |
| OOO | 1-50 | 5F10.0 | WKAPPA(4,1), ..., WKAPPA(4,5) |
| PPP | 1-50 | 5F10.0 | WKAPPA(5,1), ..., WKAPPA(5,5) |

| | | | |
|---|---|---|---|
| QQQ | (Included only if IHAZRD = 6.) | | |
| QQQ | 1-80 | 8F10.0 | WBASE(1), ..., WBASE(N) |
| RRR | (Included only if ICRISK = 1.) | | |
| RRR | 1-10 | F10.0 | ATAU |
| | 11-20 | F10.0 | KK |
| | 21-30 | F10.0 | W |
| SSS | 1-10 | F10.0 | PART |
| TTT | 1-10 | F10.0 | TTERM |
| UUU - WWW | (Included only if ITSACR = 1.) | | |
| UUU | 1-50 | 10I5 | NSACR(1), ..., NSACR(N) |
| VVV | 1-50 | 10F5.0 | TSACR(i,1), ..., TSACR[i,NSACR(i)] |
| WWW | 1-80 | 16I5 | NTSACR(i,1), ..., NTSACR[i,NSACR(i)] |
| XXX - YYY | (Included only if JPART = 1.) | | |
| XXX | 1-2 | I2 | NTPART |
| YYY | 1-80 | 8F10.0 | TPART(1), ..., TPART(NTPART) |
| ZZZ | 1-8 | | IY |

# Appendix C

## Computation of Initial Estimates of Model Parameters

The user of MRS. T 1981 may specify initial estimates of the model parameters $\alpha$, $\beta$, and $\delta$ or may request that the program compute its own initial estimates. The user may specify initial estimates for (1) all three of $\alpha$, $\beta$, $\delta$, (2) only two of $\alpha$, $\beta$, $\delta$ (3) only one of $\alpha$, $\beta$, $\delta$ or (4) none of $\alpha$, $\beta$, $\delta$. Since $\alpha$, $\beta$, and $\delta$ are vectors, the user must specify all of the vector and not just part of the vector. For example, if $\beta = [\beta_1, \ldots, \beta_r]$, then $\beta_1, \ldots, \beta_r$ must all be specified if any one is specified. The only exception to this rule is that $\alpha_0$ can be specified as $\alpha_0 = 0$ without specifying the rest of the $\alpha$ vector. If $\alpha_0 = 0$, then $P(T,0) = 0$ for all T; so that, specifying $\alpha_0 = 0$ implies that the response never occurs spontaneously; that is, the response never occurs when $d = 0$.

If any initial estimates are specified by the user, these initial estimates will be used for all groups, $g = 1, \ldots, G$. If $G > 1$ and the user has requested that an initial estimate be computed by the program, then a separate initial estimate will be computed for each group and the combination of all groups.

If an initial estimate of $\delta$ is not specified, then the program uses $\delta \equiv 0$ as its initial estimate of $\delta$.

The program computes initial estimates of $\alpha$ and/or $\beta$ under the assumption that $\delta \equiv 0$ even though another initial estimate of $\delta$ may have been specified and will be used at the beginning of the sequential search for the restricted maximum likelihood estimates of $\alpha$, $\beta$, and $\delta$.

If the user has requested that the program compute its own initial estimate of $\alpha$, then the initial estimate of $\alpha$ is determined as follows. If $\alpha_0$ has been specified as zero, $\alpha_0$ is fixed equal to zero; otherwise, $\alpha_0$ is treated like the rest of the $\alpha$ vector. For each dose level $d_i$, $i = 1, \ldots, D$, let

$p_i$ = the observed proportion of experimental units at dose $d_i$ which have had a response (C.1)

and

$$y_i = \ell n(1.0 - p_i) \ . \qquad \text{(C.2)}$$

If

$$P(T,d) = 1\text{-}\exp\{-g(d;\alpha)H(T;\beta,\delta)\} \ , \qquad \text{(C.3)}$$

then

$$\begin{aligned} y &= \ell n[1.0-P(T,d)] = g(d;\alpha)H(T;\beta,\delta) \\ &= H(T;\beta,\delta) \sum_{s=0}^{a} \alpha_s d^s \ . \end{aligned} \qquad \text{(C.4)}$$

The $p_i$ in (C.1) just reflects the occurrence of a response and not the specific time of the occurrence; hence, $p_i$ is roughly the proportion of responses by the largest observation time, say TFINAL. Thus, $y_i$ in (C.4) refers to $T$ = TFINAL and $d = d_i$; that is,

$$y_i \doteq H(\text{TFINAL};\beta,\delta) \sum_{s=0}^{a} \alpha_s d_i^s \ . \qquad \text{(C.5)}$$

The initial estimates of the $\alpha_s$* H(TFINAL;$\beta,\delta$)'s are then obtained by minimizing

$$\sum_{i=1}^{D} (y_i - \sum_{s=0}^{a} [H(TFINAL;\beta,\delta)\alpha_s]d_i^{\,s})^2 \qquad (C.6)$$

subject to the restriction

$$[H(TFINAL;\beta,\delta)\alpha_s] \geq 0 \quad . \qquad (C.7)$$

If an initial estimate of $\beta$ has been specified by the user to be $\overset{\approx}{\beta}$ then the initial estimates of the $\alpha_s$'s are

$$\tilde{\alpha}_s = [H(\widehat{TFINAL;\beta,\delta})\alpha_s]/H(TFINAL;\overset{\approx}{\beta},\delta\equiv 0) \ . \qquad (C.8)$$

If the initial estimate of $\beta$ has not been specified by the user, then the initial estimates of the $\alpha_s$'s are

$$\tilde{\alpha}_s = [H(\widehat{TFINAL;\beta,\delta})\alpha_s]*\sum_{r=1}^{b} \overset{\approx}{\beta}_r \qquad (C.9)$$

where the $\overset{\approx}{\beta}_r$'s are the unscaled estimates of the $\beta_r$'s discussed in the next paragraph.

If the user has requested that the program compute its own initial estimate of $\beta$, then the initial estimate of $\beta$ is determined as follows: Let

TEARLY = smallest observation time,

TFINAL = largest observation time,

and

$$t_k = TEARLY + k*(TEARLY-TFINAL)/10.0 \qquad (C.10)$$

for $k = 1, 2, \ldots, 10$. For each dose level, $d_i$, $i = 1, 2, \ldots, D$, let

$p_{i\ k}$ = the observed proportion of experimental units at dose $d_i$ which have had a response detected before $t_k$

for $k = 1, 2, \ldots, 10$. Let $a_s$ be either the initial estimate of $\alpha_s$ specified by the user or

$$a_s = [H(\widehat{TFINAL;\beta,\delta})*\alpha_s] \qquad (C.11)$$

determined in (C.6) and (C.7) if no initial estimate of $\alpha_s$ has been specified. Let $\underline{a}$ be the vector containing the $a_s$'s. Let

$$y_{ik} = -[\ell n(1.0 - p_{ik})]/g(d_i;\underline{a}) \qquad (C.12)$$

for $i = 1, \ldots, D$ and $k = 1, \ldots, 10$. If

$$P(T,d) = 1-\exp\{-g(d;\alpha)H(T;\beta,\delta)\} \qquad (C.13)$$

then

$$\begin{aligned} y &\dot{\equiv} -[\ell n(1.0-P(T,d))]/g(d;\alpha) \\ &= H(T;\beta,\delta) \quad . \end{aligned} \qquad (C.14)$$

Now, $g(d_i;\underline{a})$ is approximately $g(d_i;\alpha)$ except for a scale constant C which arises since the $\beta$'s in the model are (without loss of generality) scaled so that $\sum_{r=1}^{b} \beta_r = 1$. Thus,

$$y_{ik} \doteq H(t_k;\beta,\delta)/C \ . \qquad (C.15)$$

The unscaled estimates of the $\beta_r$'s are the $\approx{\beta}_r$'s which minimize

$$\sum_{i=1}^{D} \sum_{k=1}^{10} [y_{ik} - H(t_k;\underset{\sim}{\overset{\approx}{\beta}},0)]^2 \qquad (C.16)$$

subject to the restriction

$$\overset{\approx}{\beta} \geq 0 \quad . \qquad (C.17)$$

The initial estimates of the $\beta_r$'s are

$$\tilde{\beta}_r = \overset{\approx}{\beta}_r \Big/ \sum_{r=1}^{b} \overset{\approx}{\beta}_r \quad . \qquad (C.18)$$

## APPENDIX D

## ARRAY DIMENSIONS IN THE PROGRAM

In the list of arrays below, the following apply:

N = the number of dose levels including the 0 dose level, $N \leq 10$ ;

G = the number of groups, $G \leq 10$ ;

J = the maximum number of observations at any dose level in any group, $J \leq 150$ ;

LMAX = the maximum number of observations per dose level when all groups are combined, $\text{LMAX} \leq 600$ ;

LORDER = the maximum order of the dose polynomial $g(X;\alpha)$ , $\text{LORDER} \leq 10$ ;

LTRUE = the maximum order of the dose polynomial used in simulating times to tumor, $\text{LTRUE} \leq 9$ ;

NBETA = the maximum order of the time polynomial $H(t;\beta)$ ; $\text{NBETA} \leq 10$ ;

NCTIME = the number of specified times T in Tables B.1 and B.3 , $\text{NCTIME} \leq 40$ ;

NDMFP = the number of dose levels d for which mean free periods are to calculated for Table C.3 , $\text{NDMFP} \leq 50$ ;

NDTIME = the number of specified times T in Table A.4, $\text{NDTIME} \leq 40$ ;

NLATET = the number of times $t^{**}$ to be used in defining the late risk dose, $\text{NLATET} \leq 50$ ;

NMAXP = the number of maximum periods $t^{*}$ in Table C.3, $\text{NMAXP} \leq 5$ ;

NMFDMP = the number of maximum periods $t^{***}$ used in defining the mean free dose, $\text{NMFDMP} \leq 50$ ;

NPINC = the number of permissable increments considered in the definitions of the virtually safe dose, $\text{NPINC} \leq 5$ ;

NRISKD = the number of dose levels d in Table C.2, $\text{NRISKD} \leq 50$ ;

NTPART = the number of possible times on the partitioned time scale in the simulation, $\text{NTPART} \leq 40$ ;

NTSACR = the number of sacrifice times in the simulation, $\text{NTSACR} \leq 40$ ;

NTSTAR = the number of times $T^*$ considered in the definitions of of the virtually safe dose, NTSTAR $\leq 5$ ;

NXS = the number of specified doses d in Table C.1, NXS $\leq 10$ ;

NXTIME = the number of specified times in Tables B.2 and B.4, NXTIME $\leq 40$ ;

S = LORDER + NBETA + N , S $\leq 30$ ;

TIME = the maximum number of observation times at a dose level in a group, TIME $\leq 40$ ;

1. Arrays in COMMON Statements:

AC (LORDER + 1)

AINT (LORDER + 1)

ALPHAS (G, LORDER + 1)

BESTX (S)

BETAS (G, NBETA)

BINT (NBETA)

CTIME (NCTIME)

DELTAS (G, N)

DINT (N)

DTIME (NDTIME)

DIRECT (S,S)

DMFP (NDMFP)

ELRD(G, NLATET, 10)

ELRDCL (G, NLATET, 10)

EMFD (G, NMPDMP, 10)

EMFDCL (G, NMPDMP, 10)

EVSD (G, NPINC, NTSTAR)

EVSDCL (G, NPINC, NTSTAR)

FRAC (S)

GBOUND (G,N)

GSPACE (S)

H (S,S)

HDPOLY (TIME or LMAX, N)

HPOLY (TIME or LMAX, N)

IDEST (4)

IDIMP (3)

IDLRDT (5)

IDMFDT (5)

IDOBS (5)

IDVSDT (5)

INGPTS (S)

ISTOP (10)

* IT (G, J, N)

ITHETA (NBETA)

L (G + 1, N)

NGPTS (S)

NITD (G + 1, 3, N)

NPERD (N)

NPDT1 (N)

NPDT2 (N)

NRT (G, N, TIME, 3)

NSACR (N)

NTIME (G,N)

NTSACR (N, NTSACR)

* OBS (G, J, N)

PINC (NPINC)

RISKD (NRISKD)

RISKL (10)

RLATEF (10)

RLATET (NLATET)

RMFDMP (NMFDMP)

RMFDP (10)

RTIME (G, N, TIME)

SFRAC (S)

SGSPAC (S)

SH (S,S)

SWFRAC (S)

T (9)

TIMMIN (G,N)

TLRD (NLATET, 10)

TMFD (NMFDMP, 10)

TMFP (5)

TPART (NTPART)

TSACR (G, NTSACR)

TSTAR (NTSTAR)

TVSD (NPINC, NTSTAR)

WALPHA (LTRUE + 1)

WBASE (10)

WBETA (10)

WFRAC (S)

WKAPPA (6,5)

X (N)

XINT (S)

XDIREC (S,S)

XS(NXS)

XTIME (NXTIME)

Y (N)

YY (9N)

* ZAVIT (LMAX, N)

ZAVNRT (N, TIME, 3)

ZAVNT (N)

* ZAVOBS (LMAX, N)

ZAVRT (N,TIME)

ZGBND (N)

ZTMIN (N)

The arrays preceded by an * only need to be fully dimensioned if JREAD = 0 .

## 2. Arrays not in COMMON Statements

| Subroutine or Function: | Array: |
|---|---|
| CALLRD | A(LORDER + 1) |
| | AA(MAX[NBETA + 1, LORDER + 1]) |
| | B(NBETA) |
| CALMFD | A(LORDER + 1) |
| | B(NBETA) |
| | G(N) |
| CALVSD | AHOLD(LORDER + 1) |
| | BHOLD(NBETA) |
| | DHOLD(N) |
| DEMP | ADELTA(N) |
| | ALPHAA(LORDER + 1) |
| | BETAA(NBETA + 1) |
| | SDALPH(LORDER + 1) |
| | SDBETA(NBETA + 1) |
| | SDDELT(N) |
| DSIMP | Y(201) |
| FUNCLS | Y(201) |
| | A(LORDER + 1) |
| | B(NBETA) |
| | G(N) |
| FUNCT | POINT(S) |
| FUNCT1 | ALPHA(LORDER + 1) |
| | BETA(NBETA) |
| | DALPHA(LORDER + 1) |
| | DBETA(NBETA) |
| | DDELTA(N) |
| | DELTA(N) |
| | POINT(S) |
| FUNCT2 | ALPHA(LORDER + 1) |
| | BETA(NBETA) |
| | DALPHA(LORDER + 1) |
| | DBETA(NBETA) |
| | DDELTA(N) |
| | DELTA(N) |
| | POINT(S) |

| | |
|---|---|
| FUNCT4 | ALPHA(LORDER + 1)<br>BETA(NBETA)<br>DALPHA(LORDER + 1<br>DBETA(NBETA)<br>DDELTA(N)<br>DELTA(N)<br>POINT(S) |
| FUNCT5 | ALPHA(LORDER + 1)<br>BETA(NBETA)<br>DALPHA(LORDER + 1)<br>DBETA(NBETA)<br>DDELTA(N)<br>DELTA(N)<br>POINT(S) |
| FUNCT7 | POINT(S) |
| FUNCT8 | HH(9)<br>POINT(S)<br>TBETA(NBETA) |
| GXALPH | A(LORDER + 1) |
| GDBLE | A(LORDER + 1) |
| HDBETA | B(NBETA) |
| HDBLE | B(NBETA) |
| HDDBLE | B(NBETA) |
| HROOT | B(NBETA) |
| HTBETA | B(NBETA) |
| H2ROOT | B(NBETA) |
| INITB | G(N)<br>NBT(N,9)<br>P(N,9) |
| MAIN | TITLE(20) |
| MLE | ALPHA(LORDER + 1)<br>BETA(NBETA)<br>DELTA(N)<br>XBETA(NBETA)<br>XDELTA(N) |

| | |
|---|---|
| PARAM | ALPHA(LORDER + 1)<br>BETA(NBETA)<br>DELTA(N)<br>POINT(S) |
| PLRDCR | TEMP(10) |
| PLRDR | TEMP(10) |
| PLRDTR | TEMP(10) |
| PMFDCR | TEMP(10) |
| PMFDR | TEMP(10) |
| PMFDTR | TEMP(10) |
| POLYR | A(MAX[NBETA + 1, LORDER + 1]) |
| PRINT4 | ALPHA(LORDER + 1)<br>BETA(NBETA)<br>DELTA(N) |
| PVSDCR | TEMP(NTSTAR) |
| PVSDR | TEMP(NTSTAR) |
| PVSDTR | TEMP(NTSTAR) |
| TABA23 | INDEX(N) |
| TABA4 | NBTIME(N,NDTIME)<br>NTOTAL(N,NDTIME)<br>PBTIME(N,NDTIME) |
| TABB1 | A(LORDER + 1)<br>B(NBETA)<br>G(N)<br>GGG(N)<br>OBTIME(N,NCTIME)<br>PCTIME(N,NCTIME) |
| TABB2 | A(LORDER + 1)<br>B(NBETA)<br>G(N)<br>GGG(N)<br>OBTIME(N,NCTIME)<br>PCTIME(N,NCTIME) |
| TABB3 | A(LORDER + 1)<br>B(NBETA)<br>G(N)<br>GGG(N)<br>OBTIME(N,NXTIME)<br>PCTIME(N,NXTIME) |

| | |
|---|---|
| TABB4 | A(LORDER + 1)<br>B(NBETA)<br>G(N)<br>GGG(N)<br>OBTIME(N,NXTIME)<br>PCTIME(N,NXTIME) |
| TABC1 | A(LORDER + 1)<br>B(NBETA)<br>G(N)<br>GD(NXS)<br>PHAT(NXS) |
| TABC2 | A(LORDER + 1)<br>B(NBETA)<br>G(N)<br>GD(NRISKD)<br>THAT(10) |
| TABC3 | A(LORDER + 1)<br>B(NBETA)<br>G(N) |
| TMFP | Y(201)<br>WCOEF(5) |

All arrays in the following subroutines have either dimension S or fixed dimensions:

GRAD, SEARCH, FIBO, EQUINT, EQUINT3, DICHOT, QUADLS, INTVAL, GRID, POWELL, UNIVAR, STEEP, FLTPOW, PSTOP, PLINE, SLINE, STOPS.

ROBERT LEWIS SIELKEN, JR.

## RESUME

June, 1982

## I. Personal Information

U. S. Citizen

Home Address:
1811 Hondo Drive
College Station, Texas 77840

Office Address:
Institute of Statistics
Texas A&M University
College Station, Texas 77843

Wife: Jane

Children: Robert Selby Sielken, 7; Andrea Jane Sielken, 5.

## II. Academic Qualifications

Ph.D. in Probability and Statistics, Florida State University, June 1971

M.S. in Probability and Statistics, Florida State University, March 1968

B.A.,Mathematics major, DePauw University, June 1966

NDEA Fellowship (3 yrs.), Biometry Trainee, Rector Scholar (Fellowship), Phi Beta Kappa, Phi Kappa Phi

## III. Positions Held

Institute of Statistics, Texas A&M University: Assistant Professor, January 1971 to September 1976.

Institute of Statistics, Texas A&M University: Associate Professor, September 1976 to September 1982.

Institute of Statistics, Texas A&M University: Professor, Effective September 1982

## IV. Memberships in Societies

The Mathematical Programming Society,
The Operations Research Society of America.
The Institute of Management Sciences,
Southeast Texas Chapter of the American Statistical Association,
The American Statistical Association,
The Biometric Society, and
The Institute of Mathematical Statistics.

V. Publications

1. "Stopping Times for Stochastic Approximation Procedures," Zeitschrift fur Wahrscheinlichkeitstheorie und verwandte Gebiete, 26, 1973, 67-75.

2. "Sequential Sampling and Maximum Likelihood Estimation," Communications in Statistics, 1, 1973, 567-568.

3. "Two Linear Programming Algorithms for Unbiased Estimation of Linear Models," Journal of the American Statistical Association, 68, 1973, 638-641, (with H. O. Hartley).

4. "A 'Super-Population Viewpoint' for Finite Population Sampling," Biometrics, 31, 1975, 411-422, (with H. O. Hartley).

5. "Sequencing with Setup Costs by Zero-One Mixed Integer Linear Programming," AIIE Transactions, September, 1976, 369-371.

6. Book Review: Practical Linear Programming with Computer Applications, by Michael O. Locks. Technometrics, 17, 1975, 514.

7. "Estimation of 'Safe Doses' in Carcinogenic Experiments," Biometrics, 33, 1977, 1-30, (with H. O. Hartley).

8. "Critical Path Analysis in Stochastic Networks: Statistical PERT," SCIMA 6, No. 3, 1977, (with H. O. Hartley and E. Arseven).

9. "Response to Prof. Mantel's Discussion of Presentation by Hartley and Sielken on the Estimation of 'Safe Doses' and Carcinogenic Experiments," Journal of Environmental Pathology and Toxicology, 1, 267-269, 1977, (with H. O. Hartley).

10. "Exact Confidence Limits for Linear Combinations of Variance Components in Nested Classifications," Journal of American Statistical Association, 73, 1978, 632-635, (with R. K. Burdick).

11. "Variance Estimation Based on a Super-Population Model in Two-Stage Sampling," Journal of the American Statistical Association, 74, 1979. (with R. K. Burdick).

12. "A New Statistical Approach to Project Scheduling," Decision Information, ed. by C. P. Tsokos and R. M. Thrall, 1979, 153-184, (with H. O. Hartley).

13. "On Estimating a Discrete Distribution Function with Some Jump Sizes Known," Communications in Statistics, B10(2), 109-128, 1981, (with T. C. Baker, Jr.).

14. "Estimation of a Distribution Function by Extrapolating Upper and Lower Bounds," *Communications in Statistics*, B10(1), 77-93, 1981, (with T. C. Baker, Jr.)

15. "The Product Form of the Hazard Rate Model in Carcinogenic Testing," *Statistics and Related Topics*, 185-200, 1981. M. Csorgo, D. A. Dawson, J. N. K. Rao, and A. K. Md. E. Saleh (eds.), North Holland, New York (with H. O. Hartley and H. D. Tolley).

16. "Re-Examination of the ED$_{01}$ Study-Risk Assessment Using Time," *Fundamental and Applied Toxicology*, *1*, 88-123, 1981.

17. "Which Options Provide the Quickest Solution," *Evaluating Mathematical Programming Techniques*, 135-145, 1982. Edited by John M. Mulvey. Volume 199 in *Lecture Notes in Economics and Mathematical Systems*, Springer-Verlag, New York.

18. "A Comparison of Statistical Methods for Low-Dose Extrapolation Utilizing Time to Tumor Data," *Fundamental and Applied Toxicology*, 1982 (to appear with D. Krewski, K. S. Crump, D. W. Gaylor, C. Portier, D. Salsburg, and J. Van Ryzin).

VI. Computer Algorithms Implemented

1. Optimal Investment Strategies in Shrimp Fishing

2. Linear Programming Algorithms
   a. Revised Simplex Standard Form I and II
   b. Dual Simplex Method
   c. Primal-Dual Method
   d. Primal-Dual Transportation Algorithm
   e. Decomposition Algorithm

3. Unbiased Estimation of Linear Models by Minimizing the Sum of the Absolute Residual or Minimizing the Maximum Absolute Residual
   a. MRS. A
   b. MR. A

4. Analysis of Univariate Time Sweies Data Using the Methods of Box and Jenkins
   a. Identification
   b. Estimation, Diagnostic Checking, and Forecasting
   c. Time Series Generator
   d. Theoretical Autocorrelation and Partial Autocorrelation Determination

5. Solving Transportation Problems Involving Source-Location Optimization

6. Confidence Limits for Global Optima

7. All Integer Programming Algorithm
   a. Balas' Procedure
   b. New Procedure (SLIP)

8. Mixed Integer Programming Algorithms
   a. Dakin's Procedure
   b. Davis-Kendrick-Weitzmann Procedure
   c. Tomlin-Gomory Procedure
   d. Geoffrion's Method of Surrogate Constraints
   e. New Procedure (BABAT)

9. Statistical PERT Algorithms
   a. Deterministic Project Scheduling
   b. Stochastic Project Scheduling

10. Quadratic Programming Algorithm

11. Unconstrained Optimization Algorithm
    a. Univariate Search
    b. Grid Search
    c. Pattern Search
    d. Powell's Method
    e. Steepest Ascent
    f. Fletcher-Powell Method

12. Statistical Methodology for Toxicological Research
    a. MRS. T
    b. MRS. T 1981

13. Determination of Sample Sizes to Meet Variance Restrictions (NASA).

14. Determination of Crop Acreages from Multiyear Satellite Sampling (NASA).

## VII. Teaching Experience

Institute of Statistics, Texas A&M University, 1971 - present.

Areas:

a. Mathematical Programming: linear, nonlinear, and integer programming
b. Undergraduate and graduate introductions to probability and statistics
c. Probability
d. Limit Theory
e. Statistical Inference
f. Decision Theory
g. Sequential Analysis
h. Time Series Analysis

Specific Courses:

Stat. 211 Principles of Statistics I. (Spring 1976 - 2 sections, Spring 1980, Fall 1980, Spring 1981)

Stat. 302 Statistical Methods. (Fall 1976)

Stat. 410 Optimization. (Fall 1974, Spring 1976, 1977, 1979, 1981)

Stat. 414 Mathematical Statistics. (Spring 1971, Fall 1978)

Stat. 601 Statistical Analysis. (Summer 1973, Fall 1973, Spring 1974, Fall 1974, Fall 1981)

Stat. 602 Statistical Analysis. (Fall 1971 - 2 sections, Fall 1972, Spring 1973)

Stat. 610 Theory of Statistics I. (Fall 1977)

Stat. 611 Theory of Statistics II. (Spring 1975)

Stat. 614 Advanced Theory of Statistics. (Spring 1977, 1978, 1979, 1980)

Stat. 621 Advanced Topics in Statistical Theory. (Summer 1971)

Stat. 626 Statistical Methods of Process Control and Optimization. (Summer 1976, 1978, 1980)

Stat. 628 Mathematical Programming I. (Spring 1972, 1973, 1974, 1975, 1976, Fall 1976, 1977, 1980)

Stat. 629 Mathematical Programming II. (Summer 1972, 1974, 1975, 1977, 1979, 1981)

Stat. 632 Statistical Decision Theory. (Fall 1972, 1975)

Stat. 651. Statistics in Research I. (Spring 1982, Summer 1982)

## VIII. Contract Activities

1. National Center for Toxicological Research and Food and Drug Administration

Participation: 2 years

General Area: Statistical techniques for the estimation of carcinogenic risk based on animal experiments.

Technical Reports:

#1 "A Parametric Model for 'Safety' Testing of Carcinogenic Agents" by H. O. Hartley and R. L. Sielken Jr.

#2 "A'Non-Parametric' Model for 'Safety' Testing of Carcinogenic Agents" by H. O. Hartley and R. L. Sielken Jr.

#3 "The General 'Product Model' for Time to Tumor Distributions" by H. O. Hartley

#4 "Computational Experience in 'Safety' Testing of Carcinogenic Agents" by R. L. Sielken Jr.

2. Sea Grant

Participation: 1 year

General Area: Application of mathematical programming techniques to management problems in the shrimp fishing industry.

Technical Report:

"Extended Results on Optimal Investment Strategies in Shrimp Fishing" by R. L. Sielken Jr., R. G. Thompson, R. R. Wilson, December, 1972.

3. NASA

Participation: 5 years

Principal Investigator: 2½ years

General Area: Application of statistical and operations research techniques to satellite based estimation of crop acreages.

Procedures: nonlinear programming, ANOVA, variance components, sampling design, partial identification.

Technical Reports:

#17 "A Computer Implementation of the Multicrop Sampling Strategy" by H. O. Hartley, T. H. Hughes, R. L. Sielken, Jr., May 1979.

#18 "Optimal Rotation Designs for Multiyear Estimation, I. Unweighted Estimation," by E. E. Gbur and R. L. Sielken, Jr., December 1980.

#19 "Optimal Rotation Designs for Multiyear Estimation, II. Weighted Estimation," by E. E. Gbur and R. L. Sielken, Jr., December 1980.

#20 "Multiyear Estimation of the At Harvest Crop Acreage Proportion: Methodology and Implementation," by Robert L. Sielken, Jr. and Paul F. Dahm. March 1981.

#21 "Incorporating Partially Identified Sample Segments Into Acreage Estimation Procedures: Estimates Using Only Observations From The Current Year," by Robert L. Sielken, Jr., December 1981.

#22 "Missing Observations in Multiyear Rotation Sampling Designs," by E. E. Gbur and R. L. Sielken, Jr., December 1981.

### 4. Office of Naval Research

Participation: 10 years

Principal Investigator: 1 1/2 years

General Area: The interface between operations research, management science, and statistics particularly optimization techniques.

Technical Reports:

| | | |
|---|---|---|
| #41 | August 1972 | UNBIASEDNESS IN LINEAR MODEL ESTIMATION<br>R. L. Sielken Jr. and H. O. Hartley |
| #42 | August 1972 | A TRANSPORTATION PROBLEM INVOLVING SOURCE-LOCATION OPTIMIZATION<br>R. L. Sielken Jr. |
| #43 | August 1973 | CONFIDENCE REGIONS FOR GLOBAL OPTIMA IN NON-LINEAR PROGRAMMING<br>T. L. Liau, H. O. Hartley and R. L. Sielken Jr. |
| #44 | September 1973 | THE ITERATIVE ALGORITHM FOR SOLVING "A TRANSPORTATION PROBLEM INVOLVING SOURCE-LOCATION OPTIMIZATION"<br>R. L. Sielken Jr. |
| #48 | November 1974 | STATISTICAL CRITICAL PATH ANALYSIS IN ACYCLIC STOCHASTIC NETWORKS: STATISTICAL PERT<br>R. L. Sielken Jr., L. J. Ringer, H. O. Hartley, E. Arseven |
| #50 | January 1976 | STATISTICAL PERT: DECOMPOSING A PROJECT NETWORK<br>R. L. Sielken Jr., Norman E. Fisher |
| #51 | January 1976 | STATISTICAL PERT: AN IMPROVED SUBNETWORK ANALYSIS PROCEDURE<br>R. L. Sielken Jr., H. O. Hartley and R. K. Spoeri |
| #52 | November 1975 | INCORPORATING PROJECT COST CONSIDERATIONS INTO STOCHASTIC PERT<br>Paul P. Biemer and R. L. Sielken Jr. |
| #53 | April 1976 | A STATISTICAL PROCEDURE FOR OPTIMIZATION OF PERT NETWORK SCHEDULING SYSTEMS<br>R. K. Spoeri, L. J. Ringer and R. L. Sielken Jr. |
| #55 | February 1977 | STATISTICAL PERT: AN IMPROVED PROJECT SCHEDULING ALGORITHM<br>Cynthia S. Dunn and R. L. Sielken Jr. |

| | | |
|---|---|---|
| #56 | December 1977 | A NEW STATISTICAL APPROACH TO PROJECT SCHEDULING<br>R. L. Sielken Jr. and H. O. Hartley |
| #57 | August 1978 | A USER'S GUIDE TO THE COMPUTER IMPLEMENTATION OF THE NEW PROJECT SCHEDULING PROCEDURE: STATISTICAL PERT<br>Thomas C. Baker, Jr. and Robert L. Sielken Jr. |
| #58 | August 1978 | STATISTICAL PERT: IMPROVEMENTS IN THE DETERMINATION OF THE PROJECT COMPLETION TIME DISTRIBUTION<br>Thomas C. Baker, Jr. and Robert L. Sielken Jr. |
| #59 | September 1980 | MULTIVARIATE EDGEWORTH AND GRAM-CHARLIER EXPANSIONS AND THEIR APPLICATIONS TO STATISTICAL PERT<br>Christian C. Robieux, H. O. Hartley, Frederic C. Lam, R. L. Sielken Jr. |
| #60 | September 1980 | STATISTICAL PERT: THE PRECISION OF THE ESTIMATED PROJECT COMPLETION TIME DISTRIBUTION<br>Christian C. Robieux, H. O. Hartley, Frederic C. Lam, R. L. Sielken Jr. |
| #61 | September 1978 | PROJECT SCHEDULING WITH DISCONTINUOUS PIECEWISE CONVEX ACTIVITY COST FUNCTIONS<br>Christian C. Robieux and Robert L. Sielken Jr. |
| #62 | May 1980 | HOW NEAR IS A NEAR-OPTIMAL SOLUTION: CONFIDENCE LIMITS FOR THE GLOBAL OPTIMUM<br>Robert L. Sielken Jr., Howard M. Monroe |
| #63 | May 1980 | EVALUATION OF PRECEDENCE CRITERIA FOR PROJECT SCHEDULING UNDER RESOURCE CONSTRAINTS<br>Shi Min Chang and Robert L. Sielken, Jr. |
| #64 | June 1980 | UNBIASED $L_1$ ESTIMATORS AND THEIR COVARIANCES<br>Book, D., Booker, J., Hartley, H.O., and Sielken, R. L. Jr. |
| #65 | June 1980 | RESTRICTED $L_1$ ESTIMATORS AND THEIR COVARIANCES<br>Book, D., Booker, J. , Hartley, H.O., and Sielken, R. L. Jr. |
| #66 | September 1980 | SMOOTH NONPARAMETRIC REGRESSION BY QUADRATIC PROGRAMMING<br>H. O. Hartley and R. L. Sielken Jr. |

#67 September 1980 A COMPARATIVE STUDY OF SPLINE REGRESSION
A. Nougues and R. L. Sielken Jr.

#68 September 1980 ESTIMATING THE DISTRIBUTION FUNCTION OF A TRANSFORMED RANDOM VECTOR
T. C. Baker Jr. and R. L. Sielken Jr.

#69 September 1980 ESTIMATION OF A DISTRIBUTION FUNCTION BY EXTRAPOLATING UPPER AND LOWER BOUNDS
T. C. Baker Jr. and R. L. Sielken Jr.

5. NIH Biomedical Research Support Grant

Participation: 1 year

Principal Investigator: 1 year

General Area: Extensions of time to response based low dose cancer risk extrapolation and characterizations.

Procedures: Restricted maximum likelihood estimation, confidence limit procedures, sensitivity analyses, and alternative methods of summarizing risk.

## IX. Participation in Professional Organizations

Operations Research Society of America National Meetings
May 1971, November 1975, June 1979, May 1980, May 1981

The Institute of Management Science International Meetings
April 1972

SREB Summer Conference in Statistics
June 1972, June 1975, June 1978

International Symposium on Mathematical Programming at
Stanford University, August 1973

Joint Meetings of the IMS, ENAR, and ASA
March 1974, March 1976, March 1979, August 1980, March 1981, March 1982

Conference on The Status of Predictive Tools in Application to Safety Evaluation: Present and Future, Sponsored by National Center for Toxicological Research and National Institutes of Health, November 1976 and October 1977

Discrete Optimization 77
International Symposium on Integer Programming at University of British Columbia, August 1977

Southeast Chapter of American Statistical Association
November 1975

Co-Chairman for ENAR (Biometric Society) 1980 Regional Meeting

Mathematical Programming Society's Committee on Algorithms (COAL)
Conference on Developing, Testing, and Validating Software
January 1981

National Society of Toxicology Meetings
March, 1981

Annual Technical Conference of ASQC and ASA
October 1980, October 1981

Conference on Risk Assessment in Regulating Health and Safety, Brookings Institution, May 1981

Workshop on Biological and Statistical Implications of the $ED_{01}$ Study and Related Data Bases, September, 1981

Conference for Texas Statisticians
April, 1982

X. Consulting Activities

Ebon Research Systems

Enviro-Control Inc.

Rohm and Haas Co.

U. S. Soil Inc., Bio-Systems Research

Society of Toxicologists

American Industrial Health Council

Shell Oil Company

Formaldehyde Institute

Chemical Industry Institute of Toxicology

Ciba-Geigy

Calorie Control Council

Invited Presentations

1. Estimation of "Safe Doses" in Carcinogenic Experiments. Conference on the Status of Predictive Tools in Application to Safety Evaluation: Present and Future. National Center for Toxicological Research, Food and Drug Administration, and National Institutes of Health. November, 1976. (with H. O. Hartley).

2. Stochastic Models for Carcinogenic Processes and Risk Assessment. Meeting of Southeast Texas Chapter of ASA. October, 1978.

3. Stochastic Models for Carcinogenic Processes and Risk Assessment. Joint Meeting of The Biometric Society, ASA, and IMS. April, 1979.

4. Estimating the Russian Grain Production. University of South Carolina. March, 1980.

5. How Near is a Near-Optimal Solution. Joint meeting of ORSA and TIMS. May, 1980.

6. Carcinogenic Risk Assessment: Response Models and Experimental Designs. Rohm and Haas Company. June, 1980.

7. Which Options Provide the Quickest Solution. Conference on Mathematical Programming: Testing and Validating Algorithms and Software. Committee on Algorithms (COAL), Mathematical Programming Society, U.S. National Bureau of Standards, and U.S. Department of Energy. January, 1981.

8. Risk Assessment Using Time. American Industrial Health Council, Quantitative Risk Assessment Subcommittee Meeting. February, 1981.

9. Re-Examination of $ED_{01}$ Study: Risk Assessment Using Time. Meeting of the Society of Toxicologists. March, 1981.

10. Risk Assessment Based on Time to Response. Joint Meetings of The Biometric Society and ASA. March, 1981.

11. Conference on Risk Assessment in Regulating Health and Safety. Brookings Institution, Carnegie-Mellon University, and American Petroleum Institute. May, 1981.

12. Alternative Answers to How Near is a Near-Optimal Solution. Joint Meetings of ORSA, TIMS, and CORS. May, 1981.

13. Risk Assessment Using Time. Shell Oil Company. June, 1981.

14. Formaldehyde Risk Assessment. Joint Meeting of the EPA and the Formaldehyde Institute. August, 1981.

15. Quantitative Risk Assessment Using Time. Chemical Industry Institute of Toxicology. August, 1981.

16. Workshop on Biological and Statistical Implications of the $ED_{01}$ Study and Related Data Bases. National Center for Toxicological Research, American Industrial Health Council, Society of Toxicologists. September, 1981.

17. Involving Time in Risk Assessment. Meeting of the Drug Safety Subsection of the Pharmaceutical Manufacturers Association. October, 1981.

18. Failure Time Assessments Based on Varying Durations of Accelerated Stress. 25th Annual Technical Conference. ASQC and ASA. October, 1981.

19. A Re-Examination of the $ED_{01}$ Study - Cancer Risk Assessment Using Time and the Hartley-Sielken Model. Meeting of the Ottawa Chapter of Statistical Society of Canada / American Statistical Association and Health and Welfare Canada. January, 1982.

20. Characterizing Carcinogenic Risk: A Sensitivity Analysis. Joint meetings of the Biometrics Society, ASA, the American Public Health Association, and IMS. March, 1982.

21. Empirical Behavior of Low-Dose Extrapolation Procedures Used in Cancer Risk Assessment. Conference for Texas Statisticians, Baylor University, Waco, Texas. April, 1982.

## APPENDIX 12

SEP 4 1981

MEMORANDUM

SUBJECT: Options Paper on Formaldehyde

FROM: Edward A. Klein, Director
Chemical Control Division (TS-794)

TO: Don R. Clay, Director
Office of Toxic Substances (TS-792)

By this memorandum I am forwarding to you the Options Paper on Formaldehyde. The paper reflects the general concensus of our workgroup.

The Arguments section of the paper contains arguments that could be made by an advocate of either position. We do not endorse all of them, but there is general agreement on most of them.

I strongly suggest that you hold a meeting next week to discuss the issues presented in this paper. Many of the interrelationships among the issues could be more fully described. In addition, a meeting would give you a much better flavor of the nature of the problems.

CONCURRENCES

| | ORIGINATOR | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SYMBOL | | AD | | | | | | |
| SURNAME | | Stanley | | | | | | |
| DATE | 9/4/81 | 9/4/81 | | | | | | |

OFFICIAL FILE COPY

# OPTIONS PAPER ON FORMALDEHYDE:
# TO 4(f) OR NOT TO 4(f)

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I. Key Concepts in Section 4(f)

II. Implications of Science for Policy Analysis

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V. Arguments For and Against a Section 4(f) Determination

Appendix

Technical Appendix A. Health Effects of Formaldehyde

## LIST OF TABLES

Table 1: Estimates of Numbers of Cancer Cases in Populations with Formaldehyde Exposures, Including Upper 95% Confidence Limits for Those Estimates (By Exposure Level and Population Size·Estimate).

Table 2: Estimates of Frequencies of Cancer Cases in Populations with Formaldehyde Exposures, Including Upper 95% Confidence Limits for Those Estimates, for Populations with No Estimate of Number Exposed (By Exposure Level).

Table A-1: Tabulated Summary of Carcinogenicity Studies on Formaldehyde (from OPTS Priority Review Level I, 1981).

Table A-2: Summary of Studies with Findings and On-going Studies.

## I. KEY CONCEPTS IN SECTION 4(f)

The overall purposes of section 4(f) are to identify certain candidates as high priorities for regulatory consideration and to establish a deadline for deciding whether to initiate regulatory action on high priority risks that are not "reasonable".

The scope of the risks from chemical exposure that may be subject to section 4(f) is generally the same as the overall jurisdiction of TSCA and thus overlaps some risks that may be regulated under other laws or by other agencies. Where the risks are within the core jurisdiction of EPA (under TSCA or other statutes such as the Clean Air Act, RCRA, etc.), it seems fairly clear that the section 4(f) priority status exists regardless of what statute the Agency determines is most appropriate under section 6(c) or section 9(b).

There is, however, some question about the nature of the obligations imposed upon EPA and other Federal agencies when the risk is one within the primary (although not exclusive) jurisdiction of the other agency, for example a workplace risk that could be regulated under OSHA. There is no basis for asserting that section 4(f) in any legal sense sets the other agency's priority. Nevertheless, it is fairly clear that if we formally [section 9(a)] or informally refer such a problem to another agency and they "initiate action", EPA can plausibly claim that its section 4(f) obligations have been satisfied. This is also true if the other agency makes a formal "does not present the risk" finding under section 9(a)(2)(A).

If the other agency does not believe that the problem has a high enough priority for expeditious action, but resists making a formal decision not to do so, it is unclear whether section 4(f) would compel us to act or would permit us to consider that our duties with regard to the problem had been met. [Note: Under section 9(a) the other agency has a legal obligation to respond only if we make a formal referral.]

The applicability of section 4(f) to only carcinogens, mutagens, and teratogens should be considered in developing a policy for using this section. A policy that permits most or all carcinogens to qualify as section 4(f) chemicals could limit the Agency's ability to address environmental and other human health hazards. An additional point is that the fact that a chemical may be a carcinogen, mutagen, or teratogen does not, in itself, justify a section 4(f) designation. Clearly, section 4(f) is intended to address carcinogens that present risks of special concern.

A risk for which EPA must give priority consideration under section 4(f) must be one for which "there may be a reasonable basis to conclude that" the chemical "presents or will present a significant risk of serious or widespread injury to human[s]".

These key concepts are not defined in the statute, and the legislative history of TSCA provides little direct assistance in their interpretation. As OGC has stated, application of these standards requires exercise of administrative discretion informed by Agency policy.

A determination of the applicability of section 4(f) to formaldehyde will, of course, tend to define those standards not only for formaldehyde but for future section 4(f) determinations as well. In addition, the defining of those terms in this instance may well be interpreted as setting policy with regard to the Agency's approach to potential human carcinogens.

To a large degree, the definition of the threshold terms is dependent on the Agency's interpretation of what it must do should it make a positive determination under section 4(f), i.e.

what is meant by "initiate appropriate action" to reduce the risk. For instance, section 4(f) can reasonably be interpreted so that the 4(f) "initiation of action" means the issuance of a proposed rule, and this would mean that EPA must be relatively certain that not only is there a significant risk of serious or widespread harm but that an unreasonable risk probably exists. In other words, a section 4(f) determination constitutes a rebuttable presumption that EPA willl regulate. Such an interpretation would obviously require setting a high hurdle in terms of certainty about the toxicity and exposure to the chemical, which formaldehyde may or may not meet depending on one's perception of the quality of the available data.

On the other hand, OGC has indicated that the "initiate action" requirement of section 4(f) can be interpreted as being satisfied by something short of a proposed rule or an ANPRM (even possibly a referral to another Agency or a section 9 action). This lower hurdle would be consistent with a higher degree of uncertainty as to the unreasonableness of the risks, including the risk component on which the initial section 4(f) priority was based.

The setting of a lower or higher hurdle may be accomplished through the interpretation of the terms "may be", "significant risk", "serious harm", and "widespread harm". OGC argues that the standard for saying that there may be a reason to regulate is less stringent in terms of certainty than the standard for actually promulgating a rule. However, while the word "may" usually indicates a situation that is less than certain, it might not mean substantially greater uncertainty. In addition, section 4(f) clearly sets a higher standard on the magnitude and scope of risk than the minimum that may be regulated under section 6. It therefore appears that there is some latitude to create either a lower or higher hurdle based on this wording.

A "significant risk" could mean either a high liklihood of harm or a risk that is not trivial. Other Federal programs (including EPA) combine both of these concepts in their definition of risk. The commonly used range as practical cutoffs for the level of safety (in terms of individual risk) that their regulations will try to achieve is $10^{-4}$ (1 in 10,000) to $10^{-7}$ (1 in 10,000,000). One could argue that a degree of individual risk that is not considered to be a regulatory target under other statutes is not a significant risk in a TSCA section 4(f) context. On the other hand, even where there is a significant indication of risk, unless the risk is also serious or widespread, the chemical will not qualify for section 4(f) priority consideration. Note that OGC believes that the "serious or widespread harm" finding does not require the balancing of effects against costs that an "unreasonable risk" finding under section 6 does.

The terms "serious" or "widespread" permit a wide latitude in determining a chemical's relative priority among the chemicals being considered by the Agency for regulatory attention. Among the factors that could be used are total population at risk and the estimated number of cases or deaths, a factor that takes into consideration both individual risk and levels of exposure. It may be logical to call a potential harm "serious" if it results in high levels of individual risk (1 in 10 or 1 in 100) even if the number of persons exposed is not very large. On the other hand, a "widespread" harm may not present the very high risk levels of a "serious" harm but would refer to a situation where a relatively large population would be exposed to something less than "serious" harm. If the risks presented by a chemical are neither "serious" nor "widespread" by these criteria, the risks arguably are not of the magnitude contemplated by section 4(f).

A section 4(f) determination probably should not apply to a chemical *per se*, but to a chemical in certain *exposure* situations that are likely to result in significant risks of serious or widespread harm to humans. Thus, if EPA designates a section 4(f) situation, it may properly limit the focus of its unreasonable risk assessments to those risks that are most important, without being obligated to spend resources on minor exposures. However, the scope of the focus is relevant to the Agency's ability to designate the potential harm as "widespread".

With respect to the 180 day clock, there are several alternative ways of interpreting when data is considered to be "received" for purposes of triggering the deadlines in 4(f). (Of course, the question of when data has been received becomes significant only if the information that has been received is sufficient under the section 4(f) criteria). First, data could be considered received when it first comes into physical possession of the Agency. Second, data could be considered received when it comes into possession of the immediate Office of the Administrator. Third, "receipt" could be considered to occur at the point when the Administrator decides that the section 4(f) criteria have been met. OGC is preparing a memorandum analyzing the legal implications of these alternatives.

## II. IMPLICATIONS OF SCIENCE FOR POLICY ANALYSIS

This section summarizes the major issues relating to the health effects that may result from exposure to formaldehyde. A more thorough discussion can be found in the Technical Appendix. In analyzing the available data, there are points of agreement and of disagreement between EPA staff and representatives of the Formaldehyde Institute. These are discussed below.

### Relevant Tests

There are several types of test systems used to evaluate a chemical's potential for carcinogenicity. These include: (1) long-term animal studies, in which the compound is administered at different dose levels for the greater part of the animal's lifetime to determine tumor incidence; and (2) short-term studies, in which the test compound is put into contact with cultured mammalian cells or bacteria to provide an indication as to what may occur on a cellular level in live, exposed animals. Formaldehyde, as discussed below, has been evaluated in both long and short-term test systems.

### Carcinogenicity

The Chemical Industry Institute of Toxicology (CIIT) has conducted a long-term study that provides the strongest evidence to date that formaldehyde is carcinogenic in animals.

- The CIIT study exposed rats and mice to 14.1, 5.6, and 2.1 ppm formaldehyde via inhalation. After 24 months of exposure (6 hr/day, 5 days/week), 95 rats in the high dose group and three in the intermediate group developed a rare squamous cell carcinoma of the nasal turbinates. Two mice also developed the same kind of tumors at the 14.1 ppm exposure level.

Work currently underway at New York University Medical Center supports the results of the CIIT study. The NYU research, currently in the 86 week (of 104 weeks), has found in ten nasal tumors in rats exposed to formaldehyde alone (14 ppm) and nine of the same type tumors in rats exposed to formaldehyde and hydrogen chloride gas combined. Control animals and animals exposed to hydrogen chloride gas alone have not developed tumors.

Regarding the CIIT study, both EPA staff and representatives of the Formaldehyde Institute agree on the number, type, and relative rarity of the observed tumors. Also, there is general agreement within the scientific community the study's design is adequate to evaluate formaldehyde's carcinogenicity. Three prestigious scientific groups have reviewed the design of the experiment and the available data and have concluded that formaldehyde is a carcinogen in rats and mice and may pose a carcinogenic risk to humans.

Concern over the results of the CIIT and NYU studies prompted Dr. Arthur Upton of NYU to state in a letter to Mrs. Gorsuch and Dr. Todhunter that "... formaldehyde is decisively carcinogenic in animals and ... it is likely that formaldehyde is a human carcinogen."

## Mutagenicity

Because cancer is believed to be caused by alteration of a cell's genetic material, positive mutagenesis assays using bacteria and fungi are fairly accurate indicators of a compound's potential to induce cancer in mammalian systems. EPA staff and the Formaldehyde Institute agree that formaldehyde is a mutagen based on positive results in many test systems, including the widely-used Ames test.

### Cell Transformation

Cell transformation studies are used to assess a chemical's ability to transform normal, mammalian cells into neoplastic cells. While the correlations between *in vitro* and *in vivo* results are not perfect, these cell culture systems do provide biological tools that have a mechanistic relevance to the process of carcinogenisis in living mammalian organisms. EPA staff and the Formaldehyde Institute agree that formaldehyde has been shown to be positive in several types of cell transformation tests.

## Unresolved Issues

EPA staff and the Formaldehyde Institute are in disagreement over fundamental scientific issues that relate to the carcinogenicity of formaldehyde. These are discussed below.

### Interim Results

The Formaldehyde Institute maintains that the CIIT results have not been made final, have not received peer review, and are therefore preliminary and should not be used to assess the risk associated with formaldehyde exposure. These arguments also apply to the NYU study.

EPA staff considers the CIIT to be interim rather than preliminary; that is, the results have been carefully evaluated. For example, the CIIT study is interim while the NYU study is preliminary. EPA staff believes that a final report, although desirable, is not necessary for an assessment of risk. The number of tumors in the CIIT study will not decrease. In fact, tumor incidence may increase, due to the fact that some animals were not sacrificed until 27 and 30 months. Data on these animals have yet to be reported, and it is possible that more tumors developed during those months.

Additionally, although there has been only one peer review journal article (on the 18 month interim findings), the pertinent data and experimental design of the CIIT study were carefully evaluated by: (a) the Federal Panel on Formaldehyde convened by CPSC under the auspices of the National Toxicology Program; (b) scientists at the Environmental Cancer Information Center of the Mt. Sinai Medical Center in New York; and (c) the scientists at NIOSH, OSHA, and EPA. All of these groups concluded that the CIIT bioassay met accepted standards for tests designed to evaluate the carcinogenicity of chemicals delivered via inhalation, and that the interim results are meaningful regardless of the lack of a final report.

Precedence for the use of preliminary and unpublished data may be found in actions taken under FIFRA and in TSCA's PMN process. Not to allow the use of preliminary or unpublished information where EPA scientific review of the available data indicates that a qualitative determination is quite clear-cut would severely hamper the effectiveness of both of those programs.

## Mechanism of Carcinogenisis

In the CIIT study, severe injury to the nasal mucosa of the treated animals resulted in rapid cell turnover. The Formaldehyde Institute has suggested that this, in turn inhibited the cellular mechanism for the repair of DNA. In the absence of DNA repair, cancer ensued. Thus, the Institute claims that the carcinogenic effects of formaldehyde are indirect, or epigenetic.

EPA staff believes that the weight of the evidence clearly indicates that formaldehyde's carcinogenicity is due to its direct interaction with DNA. As discussed earlier, formaldehyde has been shown to cause cellular mutations, which are due to DNA damage. These mutations in turn can lead to the neoplastic conditions demonstrated by cell transformation test systems.

High Doses

The Formaldehyde Institute believes that the 14.1 ppm dose was too high to evaluate accurately the carcinogenicity of formaldehyde. At that dose level, both rats and mice developed severe lesions of the nasal mucosa, which resulted in a high cell turnover, overloaded DNA repair mechanisms, and eventually led to cancer. Because humans would not voluntarily tolerate exposure to formaldehyde at that level, they would not experience nasal lesions and the resulting chain of events terminating in neoplasia.

EPA staff, however, believes that, because formaldehyde is a mutagen and a genotoxic carcinogen, the 14.1 ppm dose simply provides more opportunity for interaction between formaldehyde and DNA, thereby promoting tumor development. Also tumors occurred in rats at 5.6 ppm, a level that is only slightly higher than that to which many humans may be exposed.

## III. EPIDEMIOLOGIC EVIDENCE

Epidemiology studies can provide the most direct evidence of carcinogenicity in humans. However,before they can provide this evidence, the studies must meet several conditions, each of which is difficult to acheive.

a. A group of people exposed to the chemical must be identified.

b. Because of the latency period between initial exposure and subsequent appearance of disease, exposures must have occurred several decades in the past.

c. Data must be available on the group of exposed persons, the levels of their exposure, and their subsequent experience with respect to cancer.

d. The study must be designed so that it avoids or reduces sources of non-random variation that will bias or confound the results. Selection bias in the choice of study group and controls are a common source of bias; the present of other factor related to cancer incidence, such as exposure to other chemical carcinogens or cigarette smoking, may confound the results, making the contribution of the chemical under study to the observed incidence of disease difficult to evaluate.

e. The degree of increased risk, if present, must be great enough to be detectable by statistical techniques that account for random variation. The ability to detect an increased risk depends on the magnitude of the increase (potency of the carcinogen and the level of exposure), the study size and duration (person-years of follow-up), the background rate of the cancer of interest (incidence in the general population), the desired statistical significance (i.e., a significance of 0.05 means that there is a 5% chance the results were due to random variation), and the type of analysis.

Generally, even the largest and most expertly performed epidemiological studies can seldom detect increases in cancer risk of less than 10% ($10^{-1}$). However, from the public health standpoint, exposures to carcinogens may be considered problems if they increase the risk of cancer by 1 case in 1000 ($10^{-3}$) exposed persons or less, especially when there is widespread exposure to the chemical. Epidemiology studies are most able to demonstrate causality when the carcinogen is very potent (cigarette smoking and lung cancer) or causes a rare, site-specific cancer (asbestos and mesothelioma, vinyl chloride and liver angiosarcoma).

## Available Epidemiologic Evidence On Formaldehyde

Preliminary results are available for three studies that examined formaldehyde exposure and cancer [Marsh (1980), Walrath (1980), and Wong (1980)]. The Formaldehyde Institute referred to these studies to support their argument that formaldehyde did not present a risk of cancer to humans. Although the studies did find excess proportions of certain types of cancers, these excesses were not statistically significant, with the exception of skin cancer in one study. No excess of nasal or respiratory cancer was found.

Several problems in the design and conduct of these studies make the results inconclusive because of small study size (the three studies together cover fewer than 2000 deaths), poor documentation of exposure, possible multiple exposures, and study design limitations. The National Toxicology Program panel evaluated these studies and other available epidemiologic evidence and concluded that available epidemiologic studies are insufficient to assess the possibility that formaldehyde is a human carcinogen.

Eight additional studies are planned or underway, focusing on embalmers, anatomists, medical technologists, garment workers, funeral service professionals, pathologists, and chemical workers. Analysis of these studies reveal that many suffer from similar limitations. An NCI study (Blair 1980) seems to have the greatest probability of detecting an increased rate of cancer. The study group will include between 10,000 and 16,000 chemical workers and will estimate the exposure for each individual.

It should be noted that none of the studies can detect relative risks of nasal cancer less than two, since the rate of this cancer in the general population is 0.1 in 100,000. Thus, negative studies will not prove that formaldehyde is completely safe, but they would indicate that the risk of causing cancer is relatively low.

## IV. QUANTITATIVE RISK ASSESSMENT

Tables 1 and 2 give the estimated numbers and frequencies, respectively, of human cancer cases in various subpopulations exposed to formaldehyde. In using these tables, it is important to keep in mind the assumptions underlying the risk assessment used to calculate the estimates. These assumptions fall into three broad categories: those concerning the dataset used as the base for extrapolations of risk, those concerning the choice of model to be used in the extrapolation, and those concerning modifications to the risk estimates from the model chosen to more closely parallel the human situation.

### The Dataset Used as the Base for Extrapolations of Risk

a. Sacrifice data at 6, 12, and 18 months were omitted from the analysis. It was assumed that these animals would not have the same potential for developing tumors as those observed for near-lifetime periods. Inclusion of the sacrifice data would have led to a lower estimation of the risk.

b. Time-to-tumor (or death) data for those animals in the unscheduled death category prior to 24 months were unavailable and therefore excluded. Those animals dying before 24 months were assumed at risk for the entire 24 month exposure period. This leads to an lower estimation of the risk. When the actual times-to-death become available, it will be both possible and desirable to recalculate risks using such time-to-tumor models as the Hartley-Sielken General Product Model (MRST) or Crump's RANK81 model.

c. Data from the 27 and 30 month sacrifices and any unscheduled deaths after 24 months were unavailable and therefore excluded. It was assumed that the dataset up to 24 months was adequate for a preliminary extrapolation of risk. This risk estimate may be an underestimate because additional tumor-bearing animals may be identified in the final study report.

d. Male and female animal data were combined for the analysis. Based upon the animal data available up to 24 months, there were no substantial differences in tumor response by sex. It was assumed that this situation would not change for any tumor response observed after 24 months.

## Choice of Model to be Used in the Extrapolation

e. Only models that provided an adequate fit to the data in the experimental range were considered. This excluded such models as the one-hit model and simple linear regression.

f. Models that were not available in-house for use in generating risks for various environmental exposure levels were excluded from consideration. These models included the Mantel-Bryan, probit, logistic regression, Weibull (Extreme-value), and gamma-multihit models.

g. Estimates of, and upper confidence limits on, risk are presented. Upper confidence limits allow for the random statistical variation in the experimental data.

h. Five percent error rates (95% confidence) were assumed to be acceptable in the generation of confidence limits on risk.

i. The Crump or "linearized" multistage model, finally chosen as the model for extrapolation, includes the assumptions of:

- additivity at low dose -- Cancer may be initiated through a chain of genetic or epigenetic events that may already be operative and producing background tumors in the absence of the particular chemical under test.
- approximate low-dose linearity of the upper statistical confidence limits.

This model has also been used routinely by the Carcinogen Assessment Group of EPA.

Note: The choice of 95% upper confidence limit on risk from the multistage model yields conservative (or highest) estimates. Relative to the other models now used for risk assessment, the "linearized" multistage model is, for these data, the most conservative by factors ranging from 64 to 225 for upper confidence limits. However, maximum likelihood (or point estimates) of risk from this model are in very good agreement with similar estimates from the other available models. Moreover, the variation in the choice of exposure level and subpopulation has as much of an effect on the magnitude of the number of cancer cases as the choice of maximum likelihood estimates or upper confidence limits on those estimates from the extrapolation model.

Modifications to Closely Parallel the Human Situation

j. The risk estimates were adjusted from their exposure base in the animal study to correspond to the various exposure situations for each exposed human subpopulation.

k. It was assumed that human subpopulations were exposed only for proportions of their lifetimes. The average lifetime for a human was assumed to be 70 years in these calculations. This resulted in generally lower and probably more realistic risk predictions than would have been obtained had lifetime exposure been assumed for these subpopulations. These "less-than-lifetime" risks may still overestimate human risk since the apparent (although preliminary) age distribution of tumors in the CIIT study appears nonlinear.

l. Perfect site concordance was assumed. Humans might, however, be at risk for cancer at sites other than the nasal cavity.

m. No species-to-species (animal-to-human) conversions were performed on the extrapolated risk (i.e., equipotency was assumed).

n. Carcinogenic risks predicted are assumed to be risks for tumor incidence, no deaths due to tumor formation. Further analyses will be possible when data become available indicating which tumors were lethal and which, if any, were "incidental".

o. Variability in response to the potential carcinogenicity of formaldehyde arising from such nonrandom sources as heterogeneity in human subpopulations exposed was not accounted for in the risk predictions. Such heterogeneity could be due to age, sexual, racial, and genetic differences (resistence or susceptibility) in human subpopulations. This variability is assumed to be potentially important but currently impossible to quantify.

Table 1 Estimates of Numbers of Cancer Cases in Populations with Formaldehyde Exposures, Including Upper 95% Confidence Limits for Those Estimates (By Exposure Level and Population Size Estimate)

| Exposed Population | Maximum Likelihood Estimates* | | "Linearized" Upper 95% Confidence Limits* | |
|---|---|---|---|---|
| | Low/Low** | High/High** | Low/Low** | High/High** |
| Industrial | | | | |
| Workers in iron/steel foundries | <1 | 2,340 | <1 | 2,358 |
| Pathologists | <1 | 285 | <1 | 313 |
| Embalmers/Mortuary personnel | <1 | 153 | 9 | 213 |
| Plywood/particleboard manufacturers | 2 | 32 | 11 | 65 |
| Urea formaldehyde installers/dealers | <1 | 15 | <1 | 30 |
| Formaldehyde resin producers | <1 | 2 | <1 | 7 |
| Textile producers | <1 | 2 | <1 | 5 |
| Urea formaldehyde foam producers/distributors | <1 | <1 | <1 | 1 |
| Fertilizer producers/applicators | <1 | <1 | <1 | <1 |
| Direct producers | <1 | <1 | <1 | <1 |
| Paper and paper products producers | <1 | <1 | <1 | 5 |
| Producers of rubber and miscellaneous plastics | <1 | <1 | <1 | <1 |
| Subtotal† | 2 | 2,829 | 20 | 2,997 |
| Consumer | | | | |
| Residents exposed to urea formaldehyde foam | 5,788 | 6,788 | 8,994 | 10,549 |
| Mobile home residents exposed to plywood/particleboard | <1 | 4,004 | <16 | 7,992 |
| College students | <1 | 9,310 | <3 | 9,481 |
| Biology instructors (college/university) | <1 | 505 | <1 | 514 |
| Biology instructors (high school) | <1 | 296 | <1 | 301 |
| Subtotal† | 5,788 | 20,903 | <9,013 | 28,837 |
| General | | | | |
| U.S. Population exposed to ambient air | <1 | 12 | <14,195 | 85,175 |
| Grand total† | 5,790 | 23,744 | <23,728 | 117,009 |

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*From K. Crump's multistage model computer program.

**"Low/Low" indicates lower exposure level, lower population size estimate; similarly, "high/high."

†Totals exclude or include estimates <1 according as the total is "low/low" or "high/high", thus affording a lower or an upper limit, respectively, for the possible total.

Table 2

Estimates of Frequencies of Cancer Cases in Populations with Formaldehyde Exposures, Including Upper 95% Confidence Limits for Those Estimates, for Populations with No Estimate of Number Exposed (By Exposure Level)

| Exposed Population | Maximum Likelihood Estimates* | | "Linearized" Upper 95% Confidence Limits* | |
|---|---|---|---|---|
| | Low** | High** | Low** | High** |
| **Industrial** | | | | |
| Furniture veneerers | <1/1,000,000,000 | 3/10 | 4/1,000,000 | 3/10 |
| Mushroom farmers | <9/1,000,000 | >6/100 | <2/10,000 | >6/100 |
| Workers in urea formaldehyde-insulated buildings | <9/1,000,000 | 2/1,000 | <2/10,000 | 3/1,000 |
| Molded products producers | <1/1,000,000,000 | 7/100,000 | 4/1,000,000 | 5/10,000 |
| Glue producers | 4/100,000,000 | 2/10,000,000 | 4/100,000 | 5/100,000 |
| Office Trailer Occupants | <1/1,000,000,000 | 4/100,000,000 | 4/1,000,000 | 2/100,000 |
| Producers of paving and roofing materials | 2/1,000,000,000 | 3/100,000,000 | 1/100,000 | 3/100,000 |
| Locomotive mechanics | <1/1,000,000,000 | 3/100,000,000 | 7/1,000,000 | 3/100,000 |
| **Consumer** | | | | |
| Residents exposed to urea formaldehyde foam/particleboard (unspecified or both) | -†† | 8/1,000 | -†† | 1/100 |
| Conventional home residents exposed to plywood/particleboard | -†† | 2/1,000 | -†† | 3/1,000 |
| Smokers | -§ | 5/100§ | -§ | 5/100§ |
| High school students | <1/1,000,000,000 | 3/10,000 | <8/100,000,000 | 3/10,000 |

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*From K. Crump's multistage model computer program.

**"Low" indicates lower exposure level; similarly, "high."

††Only worst-case estimate available.

§Only average estimate available.

## V. ARGUMENTS FOR AND AGAINST A SECTION 4(f) DETERMINATION

TSCA specifies that a determination under section 4(f) be based on two criteria:

- Whether the data are sufficient; and
- Whether the chemical presents a significant risk of serious or widespread harm.

The arguments for and against a section 4(f) determination for formaldehyde and the implications of our decision are discussed below.

### A DECISION THAT SECTION 4(f) APPLIES TO FORMALDEHYDE

#### A Finding That The Data Are Sufficient

a. The CIIT study found that formaldehyde caused cancer in rats at two dose levels and in mice at one dose level. Other evidence supports this finding: formaldehyde has been shown to be mutagenic in a variety of test systems; a replication of the CIIT study underway at NYU confirms the findings of cancer in rats exposed to formaldehyde.

b. Although the final report has not yet been published, the major results of the CIIT study are known. Further data and analysis may show an increase in the incidence of cancer, but the incidence will not decrease. The conclusions drawn from the study are not likely to change.

c. The results of mutagenicity tests show that formaldehyde is interacting with DNA, which indicates that it is a genotoxic carcinogen. This argues against the theory that the nasal cancers were the result of cell destruction and cell turnover caused by formaldehyde's irritant properties.

d. Three prestigious scientific groups concluded, after reviewing the conduct and results of the CIIT study and other evidence, that formaldehyde was an animal carcinogen and should be presumed to pose a cancer risk to humans. The groups are the National Toxicology Program panel, NIOSH, and the Environmental Cancer Information Center at Mt. Sinai School of Medicine. Dr. Upton, chairman of the Institute of Environmental Medicine at NYU, recently sent a letter to EPA and other Federal and private groups in support of these conclusions.

e. Although formaldehyde caused nasal cancers in rats, this may not necessarily be the site affected in humans. Many carcinogens attack different sites in different species. Although there is a low incidence of nasal cancers in the general human population, this does not preclude the occurrence of cancers at other sites.

f. Epidemiology studies done to date have not shown an increased risk of cancer in people exposed to formaldehyde. However, because of study design, small populations, or lack of exposure data, these studies are too insensitive to demonstrate whether formaldehyde is or is not a human carcinogen.

g. A large epidemiology study being done by NCI could identify an increased incidence of cancer because the study will examine large numbers of exposed workers and estimate exposure levels. However, analysis of the design of the study, which will not be completed for at least 2 years, suggests that it may not be powerful enough to assure that formaldehyde is not carcinogenic in humans. However, it may be sufficiently sensitive to indicate that the risk of cancer is relatively low.

h. Formaldehyde metabolism and its reaction with cellular components is the same in all animal species examined to date, including man. Of the 26 known human carcinogens, all but one also are animal carcinogens. The use of animal data as a predictor of human response has been endorsed by Federal agencies and many scientific groups, including the Interagency Regulatory Liaison Group and the National Cancer Institute.

i. The legislative history of TSCA indicates that Congress did not expect absolute certainty even in a regulatory context. The language and intent of section 4(f) indicate that even a somewhat greater degree of uncertainty is compatible with a section 4(f) finding.

j. Section 4(f) is intended to insure that EPA promptly initiate action when evidence suggests that a chemical poses a significant risk of harm. The Agency's response need not be regulatory in nature, but only that the chemical be made a high priority to determine whether it presents any unreasonable risks. This suggests that a high level of proof is not required.

k. There is a large body of data supporting formaldehyde's carcinogenic potential and a number of scientists have evaluated these data. It is unlikely that EPA will have better data for many other candidate chemicals than it now has for formaldehyde. Congress could not have intended that the standard of proof for section 4(f) be set so high that virtually no chemical falls within its purview.

A Finding That There Is A Significant Risk of Widespread Harm

l. Formaldehyde has a wide variety of uses, ranging from adhesives in particleboard and plywood to textiles treated with formaldehyde compounds. Exposure can occur from the use of formaldehyde-containing products as well as during their manufacture, resulting in potential worker and consumer exposure.

m. Available data clearly indicate that there is widespread exposure to formaldehyde, with sizable populations experiencing exposures nearly as high as those used in the CIIT study. Based on extrapolation from the high incidence of cancers seen in the CIIT study, the risks associated with formaldehyde use are large in magnitude and involve sizable populations throughout the country.

n. The risk assessment calculations made using standard EPA methodologies show that the risks associated with formaldehyde are significant, potentially affecting many lives. Although the models and assumptions used to derive these risk estimates yield the upper limit, the use of upper limits has withstood court challenge because it affords maximum protection to the public. Maximum likelihood estimates also have been calculated, and the numbers of people affected do not change significantly. Although true risks may be lower, actual risk figures cannot be determined; one approach is not necessarily more valid than another. Using a standard approach to assess risk allows a relative comparison of risk from chemical carcinogens to be made.

## Practical Implications For OTS

o. Because of the potential hazards from exposure to formaldehyde, several regulatory actions have already been taken on certain products. CPSC has proposed a ban of urea-formaldehyde foam insulation, and Canada has temporarily banned this product. HUD recently published an ANPR to determine the need for a standard for formaldehyde in manufactured homes. A section 4(f) designation would be consistent with these actions.

p. A decision that animal evidence alone is insufficient for making a section 4(f) determination sets dangerous precedents for future OTS actions. Epidemiology evidence is often difficult to obtain or inconclusive. Waiting, in essence, "till the bodies fall" before taking action may afford inadequate protection of the public. The legislative history of TSCA indicates that Congress did not favor dependence on epidemiologic data.

q. Section 4 test rules require that animal tests be done on chemicals when evidence of their hazard is unclear. The results of these tests become meaningless if animal studies are determined inadequate to take action. Thus, a decision that formaldehyde data are inadequate implies that substantially greater testing burdens must be placed on industry under section 4 test rules.

r. A section 4(f) designation informs the public of our concern about formaldehyde. This increases public awareness of the potential hazards of the chemical, which could result in the reduction of exposures that are easily controlled and may stimulate research to identify ways to reduce other exposures. In addition, announcing our investigation publicly will aid the Agency in obtaining vital information from the industry and the public needed to evaluate the chemical fully.

s. Although designating formaldehyde under section 4(f) may have a "blacklisting" effect, this would be equally true of any chemical designated under section 4(f) and, thus, is not by itself a rationale for deciding against a designation. Further, the potential "blacklisting" effect of a section 4(f) notice can be mitigated if we clearly explain the basis of our decision and the action we are initiating.

t. NRDC has informed the Agency that it intends to initiate a lawsuit if formaldehyde is not designated under section 4(f). In defending its action, the Agency is likely to have the meaning of the phrases "may be a reasonable basis to conclude," "significant risk," and "initiate action" defined by the courts, possibly resulting in an interpretation less favorable to the Agency. On the other hand, if formaldehyde is designated under section 4(f), it is unlikely that EPA will face an industry lawsuit. Because EPA's action would not constitute a final action, it would not generally be considered a proper subject for judicial review.

## A DECISION THAT SECTION 4(f) DOES NOT APPLY TO FORMALDEHYDE

### A Finding That The Data Are Not Sufficient

a. There is no direct evidence that formaldehyde causes cancer in humans. Completed epidemiology studies have not found any statistically significant increased incidence of cancer in people exposed to formaldehyde. Although limited, industry contends that these studies cast doubt on formaldehyde's potential carcinogenicity in humans.

b. In the case of formaldehyde, populations have been exposed for decades to the chemical. Therefore, it should be possible to identify any increased cancers due to formaldehyde through epidemiologic methods. Although it may not detect an increase in relatively rare nasal cancers, the large NCI study currently underway will be sensitive enough to establish whether formaldehyde is a significant carcinogen for humans. A determination of formaldehyde's carcinogenic risk should be delayed until the results of this study is available.

c. Although the results of the NCI study will not be available for 2 years, a delay in a section 4(f) designation will not significantly increase the risks to public health. In addition, by EPA's own calculations, the results will be ready before actual rulemaking could be completed.

d. The incidence of nasal cancers in the human population is much lower than would be expected if formaldehyde was as potent as the CIIT study would indicate.

e. Animal experiments are not always reliable predictors of human response. The animal and human systems may respond differently to formaldehyde. For example, rats and humans have different breathing patterns, affecting the dose received to target tissues. Without direct evidence that formaldehyde is presenting a risk to humans, assigning formaldehyde a high priority status may be inappropriate.

f. At 15 ppm, formaldehyde causes cell destruction and rapid cell turnover. Industry argues that this supports the view that formaldehyde acts indirectly, producing cancers as a result of its severe irritant properties.

g. The action required by section 4(f) indicates that the standard of proof should be high so that EPA addresses only those chemicals that may present very serious risks. The section states that EPA "initiate action or state that the risk is not unreasonable," implying that the chemical is presumed to present an unreasonable risk. To make the unreasonable risk determination within 180 days, the Agency must have more certainty in the toxicity and exposure information than exists at present for formaldehyde.

## A Finding That The Risk Is Not Significant

h. The data used by OTS to assess exposure are not representative; actual exposure levels are much lower. High exposures are limited to only a small population, who only are exposed intermittently to these levels. Therefore, the risks should not be considered either serious nor widespread.

i. The risk assessment methodogies used by EPA incorporate many worst-case assumptions that exaggerate the potential risks from formaldehyde exposure. The use of other, possibly more appropriate models and more accurate exposure information produces estimates of risks that are much lower than those developed by EPA.

j. Formaldehyde exposure is widespread, but EPA intends to focus its efforts only on a few areas. This would imply that, although exposure is widespread, the resulting risks are not.

## Practical Implications For OTS

k. A decision that section 4(f) requires a higher degree of certainty than formaldehyde will limit the number of chemicals meeting the 4(f) criteria in the future. Requiring a high standard of proof will enable OTS to focus its efforts on a very limited number of chemicals where the risks are most certain and severe. If a lower standard were adopted, OTS's resources might be spread too thin, and the most serious risks, including environmental hazards and effects other than carcinogenicity, teratogenicity, and mutagenicity, might not be adequately addressed.

l. Many of the exposures identified as presenting significant risks may occur in areas that are addressed more appropriately under other Acts. If other agencies enforcing these Acts do not take action on these problems, EPA may be forced to initiate action on problems not truly appropriate for TSCA authority or to make official section 9 referrals. In essence, this could result in EPA directing or influencing other Agencies' priorities.

m. Although a section 4(f) finding does not mean that EPA has established that the chemical *presents* a significant risk, but only that it *may* present a significant risk, a 4(f) designation may be misunderstood. The chemical may, in effect, be "blacklisted" without rulemaking when the evidence of its hazard is not conclusive, adversely affecting its marketability and creating problems for the affected industry. A high standard of proof would reduce this possibility.

n. If formaldehyde does appear to present potential threats to human health, OTS can choose to continue its investigation without making a section 4(f) designation. This would afford the same degree of protection to the public, while avoiding problems such as blacklisting and influencing other agencies' priorities through section 9 referrals.

o. Additional resources may be required after a more thorough investigation is completed. Section 4(f) requires that the Agency initiate action or make public a finding that the risk is not unreasonable. Even a determination that the risk is not unreasonable may ultimately be as resource-intensive as actual rulemaking. If formaldehyde appears to present less risk than other chemicals as the investigation progresses, it probably cannot be assigned a lower priority without publicly justifying this decision.

p. If a determination is made that section 4(f) is not applicable, OTS is not firmly locked into a decision that formaldehyde does not present a significant risk. This decision may be reversed if information that becomes available in the future confirms the risks to human health from exposure to formaldehyde.

# TECHNICAL APPENDIX A. HEALTH EFFECTS OF FORMALDEHYDE

In order to delineate the potential health effects of formaldehyde in humans, it is important to examine first the effects of this chemical in experimental animals and other relevant test systems and to attempt to extrapolate results from these studies to the human situation. The comparative analysis will now be discussed.

## 1. Direct Evidence for Carcinogenicity (CIIT Study)

The totality of information on the animal carcinogenicity of formaldehyde, including that in "Supportive Evidence -- Carcinogenicity" reviewed below, is given in a tabulated form in Table A-1.

The strongest and most direct evidence for the carcinogenicity of formaldehyde in animals is the CIIT study in which nasal tumors occurred in Fischer 344 rats (0 percent at 2 ppm, 1.5 percent at 6 ppm, and 44 percent at 15 ppm) and B6C3F1 mice (0 percent at 2 ppm and 6 ppm, and 2 percent at 15 ppm) exposed to the compound by the inhalation route. Additionally, preliminary results from a study currently in progress at NYU Medical College show nasal squamous cell carcinomas in rats exposed to 15 ppm of formaldehyde.

There is little disagreement that the CIIT study was conducted well and the results obtained are meaningful under the conditions of the test. Three independent scientific bodies reviewed the report and concluded that "the presently available data lend sufficient support to the view that it is prudent to regard formaldehyde as posing carcinogenic risk to humans" and that "formaldehyde is a carcinogen in rats . . . and in mice, at exposure levels comparable to those found in some home and work environments".

## Table A-1

Tabulated Summary of Carcinogenicity Studies
on Formaldehyde
(from OPTS Priority Review Level 1, 1981)

| Species | Group Size | Route | Dose or Concentration | Frequency of Exposure | Length of Exposure | Incidence of lesions | Tissue localization (histological type) | Reference |
|---|---|---|---|---|---|---|---|---|
| Fischer 344 rats | 120♂<br>120♀ | inhalation | 2.1 ppm<br>5.6 ppm | 6 hrs/day<br>5 days/week<br>- " - | 18 months (interim period)<br>- " - | "large number"<br>14 in 8 rats^a | Nasal hyperplastic/ metaplastic lesions<br>Nasal hyperplastic/ metaplastic lesions | Swenberg et al., Cancer Res. 40, 3398 (1980)<br>- " - |
| - " - | -"- | - " - | 14.1 ppm | - " - | - " - | 40^b/84 | 36 nasal squam. carc.<br>4 nasal squam. pap. | - " - |
| B6C3F1 mice^c | 120♂<br>120♀ | inhalation | 2.1 ppm | 6 hrs/day<br>5 days/week | 24 months | 0 | - " -<br>- " - | - " -<br>Swenberg and Kerns, CIIT Toxicology Conference on Formaldehyde Toxicity, Nov. 1980 |
| - " - | -"- | - " - | 5.6 ppm | - " - | - " - | 0 | | - " - |
| - " - | -"- | - " - | 14.1 ppm | - " - | - " - | "in 2 mice" | nasal tumors | - " - |
| Sprague-Dawley rats | 100♂ | inhalation | 14.7 ppm HCHO^d<br>10.6 ppm HCl | 6 hrs/day<br>5 days/week | lifetime | 27% | 25% nasal squ. carc.<br>2% nasal pap. | Laskin et al.<br>J. Natl. Cancer Inst., 1980, in |
| Syrian Golden hamsters | | inhalation | 10 ppm | 5 hrs/day<br>5 days/week | lifetime | 0^e | - " - | Nettesheim, Report of Progress FY 1976-77, NCI-DOE Cancer Prog |
| —"— | | —"— | 20 or 30 ppm | 5 hrs/day<br>1 day/week | 17weeks | 0^e | - " - | - "- |
| -"- | -"- | - " - | 30 ppm | 40 hrs/week | lifetime | 0^f | - " - | Dalbey and Nettesheim, 1980, Personal communication |
| Rabbits | 6 | oral mucosa exposure by "oral tank" | 3% formalin solution | 90 min/day<br>5 days/week | 10 months | 2/6 | grossly visible leukoplakias, showing histo features of carc. | Mueller et al., Exp. Path. 16, 36 (1978) |
| Rats^g | 10 | s.c. injection | 0.4% formalin 1 ml | weekly | 15 months | 4/10 | Sarcomas at the injection site | Watanabe et al. Gann 45, 451 (1954) |
| Rats^g | 20 | - " - | 5-40% hexamethylene tetramine 1-2 ml | weekly | "until tumor development" | 8/20 | 7 sarcomas and 1 adenoma (inj. site) | Watanabe and Sugimoto Gann 46, 365 (1955) |
| Rats and mice | -"- | oral | hexamethylene tetramine (up to 12.5g/kg) | - " - | max. 104 weeks | 3 different investigations gave negative results by this route | | Brendel, Arzneimittelforsch. (Drug Res.) 14,51 (1964). Della Porta et al., Food. Cosm. Tox. 6,707(1968); Tumori 56,325 (1970). |

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[a] 3 nasal tumors were found in this group at the terminal sacrifice at 24 months [Swenberg and Kerns, CIIT Toxicology Conference on Formaldehyde Toxicity, Nov. 1980].

[b] At terminal sacrifice at 24 months the number of nasal tumors has risen to 95 [Swenberg and Kerns, CIIT Toxicology Conference on Formaldehyde Toxicity, Nov. 1980].

[c] Preliminary results at terminal sacrifice.

[d] It is known that bis(chloromethyl)ether (BCME) is formed in the interaction between formaldehyde and HCl. However, the level of BCME formed was only 1 ppb in Laskin's experimental conditions. Furthermore, BCME causes mostly esthesioneuroepitheliomas in the nasal cavity, rather than squamous carcinomas.

[e] No macroscopically detectable nasal tumors.

[f] Studied together with diethylnitrosamine, HCHO appears to be a promoter as it increases the multiplicity of DEN-induced tumors.

[g] Controls were not clearly apparent in these reports.

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It is generally difficult to induce tumors in rodents by chemicals via inhalation. The dose administered, which is dependent on the concentration of the chemical in the inhalation chamber, is usually low, thereby reducing significantly the sensitivity of the test.* The CIIT finding of nasal cavity tumors in rodents, which has an extremely rare occurrence spontaneously, is therefore a highly significant observation. Furthermore, these tumors appeared in two species (rats and mice), although mice appeared to be less sensitive than rats. No tumors were reported at sites distal to the port of entry.

The appearance of nasal tumors in mice and rats exposed to formaldehyde does not imply that the same tumors will be observed in humans exposed to the chemical. There are several examples of chemicals which are carcinogenic to one site in one species and to a different site in another species. This disparity may also be seen between the sexes of the same species. The site of carcinogenicity for a particular chemical is dependent on several factors including tissue sensitivity, absorption, dose, hormonal imbalance, etc.

In order to provide absolute proof that a given animal carcinogen is also carcinogenic in humans, well conducted epidemiological studies are required. However, it should be noted that to date, all proven human carcinogens, with the exception of arsenic, have been found to be also animal carcinogens.

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*Consider that maximum tolerated doses (MTD) are recommended for carcinogenicity testing. The reason for using MTD is to maximize the probability of detecting the carcinogenicity of weak carcinogens in a relatively small size animal population.

## 2. Supportive Evidence for Carcinogenicity

### a. Carcinogenicity (other bioassay studies)

Two studies which provide notable supportive evidence for the carcinogenicity of formaldehyde in experimental animals are those of Watanabe et al. (1954) and Mueller et al. (1978) in which, respectively, sarcomas and carcinoma-like lesions were observed at the site of injection or site of application in rats or rabbits. The reports, however, lack sufficient information on control animals.

### b. Cell Transformation/Mutagenesis

Cell transformation assays provide additional supportive evidence for the carcinogenicity of chemicals. These methods use mammalian cells in an *in vitro* environment in order to study the capability of various agents to transform normal cells to neoplastic cells under controlled conditions. Thus, this *in vitro* carcinogen bioassay most closely resembles the chronic *in vivo* bioassay in rodents of all the short-term *in vitro* tests. Brusick et al. (1980) reported the transformation of mouse BALB 3T3 cells *in vitro* by formaldehyde concentrations as low as 0.5 micrograms per ml of culture fluid.

Formaldehyde was found to be genotoxic when tested in the L5178Y mouse lymphoma assay, in an unscheduled DNA synthesis test in human HeLa cells, and in sister chromatid assays in a Chinese hamster ovary (CHO) cell line.

*In vitro* mutagenesis assays using bacteria also provide suggestive evidence for the carcinogenicity of chemicals. Since mutations are due to DNA damage, and since neoplastic transformation is due to damage to the hereditary material of the cell, it has been considered that chemicals that are mutagenic are also likely to be carcinogenic. In fact, 80-90 percent of all mutagens are carcinogens.

Formaldehyde has been shown to be mutagenic in several in vitro assay systems using bacteria and fungi. For example, in the widely used Ames test it has been shown by three different laboratories to be mutagenic in one strain of Salmonella typhimurium (12/16/80 letter of Dorothy Canter, NTP, to Andrew Ulsamer, CPSC). Formaldehyde produces gene mutations and chromosome aberrations such as deficiencies, duplications, inversions and translocations. On the other hand, in dominant lethal studies conducted in Swiss mice, it was not found mutagenic.

### c. Studies with Analogs and Related Compounds

Results from studies with compounds which are structurally similar to formaldehyde provide additional scientific support for findings obtained with formaldehyde. For example, studies in rodents with acetaldehyde and malonaldehyde, which are higher aldehydes, also yielded a carcinogenic response at a local site (i.e. skin) or distal sites (i.e. liver, kidney, lung, rectum) to the site of administration.

Squamous cell carcinomas of the rat nasal cavity also have been induced following inhalation exposure to hexamethylphosphoramide (HMP). The carcinogenicity of HMP requires in vivo activation which liberates formaldehyde by oxidative metabolism of the methyl groups. The formaldehyde released was shown to produce DNA-protein cross-links closely similar to those produced by exogenously applied formaldehyde, which also induces nasal cavity tumors in rats.

d. Studies of the Mechanism of Action

Studies of the mechamism of biological action of chemicals may yield suggestive evidence for their carcinogenic potential. Since the neoplastic transformation is due to damage to DNA, the hereditary material, chemicals which combine with DNA are most often carcinogenic.

Formaldehyde and other aldehydes readily react with DNA and with proteins to form methylene-bridge cross-links. This cross-linking prevents DNA from properly replicating and transmitting its genetic information during cell replication. The DNA and DNA-protein cross-linking produced by formaldehyde and other aldehydes explains the mutagenic effects of these agents.

Note: The Formaldehyde Institute has suggested that in the CIIT study, severe non-neoplastic injury to the nasal mucosa of the treated animals resulted in rapid cell turnover. This, in turn, inhibited the cellular mechanisms for the repair of cross-linked DNA. In the absence of DNA repair, cancer ensued. Thus, the Institute claims, the carcinogenic effects of formaldehyde are indirect, termed epigenetic. There is however, absolutely no scientific evidence for this hypothesis in the published literature. Nor is there any evidence for an interrelationship between the presence of non-neoplastic injuries at any site in any species and cancer at the same site and species. There is, on the other hand, ample evidence for the interaction of formaldehyde with genetic material and for the etiological role of this type of interaction in carcinogenesis.

## 3. Quantitative Risk Assessment

Tables 2 and 3 give the estimated numbers and frequencies, respectively, of human cancer cases in various subpopulations exposed to formaldehyde. In using these tables, it is important to keep in mind the assumptions underlying the risk assessment used to calculate the estimates. These assumptions fall into three broad categories: those concerning the dataset used as the base for extrapolations of risk, those concerning the choice of model to be used in the extrapolation, and those concerning modifications to the risk estimates from the model chosen in order to more closely parallel the human situation.

### a. The Dataset Used as the Base for Extrapolations of Risk

- Sacrifice data at 6, 12, and 18 months were omitted from the analysis. It was assumed that animals sacrificed this much prior to the attainment of normal life expectancy (about 24-30 months) would not have the same potential for developing tumors that might otherwise have been observed if they had been allowed to survive. Inclusion of the sacrifice data would have lead to an underestimation of the risk.

- Time-to-tumor (or death) data for those animals in the unscheduled death category prior to 24 months were necessarily excluded from the analysis due to the unavailability of the data. It was assumed that animals dying before 24 months were at risk for the entire 24 month exposure period. This assumption leads to an underestimation of the risk, which cannot be corrected until the actual times-to-death of the individual animals become available. When such data become available, it will be both possible and desirable to recalculate risks using time-to-tumor models such as the Hartley-Sielken General Product Model (MRST) or Crump's

RANK81 model. Unfortunately it is, at the present time, impossible to predict the magnitude of risk that would be predicted by such analyses.

- Data from the 27 and 30 month sacrifices and any unscheduled deaths after 24 months were necessarily excluded from the analysis due to the unavailability of the data. It was assumed that the dataset up to 24 months was adequate for a preliminary extrapolation of risk. However, this risk estimate may be an underestimate given that additional tumor bearing animals may be found when the final study report becomes available.

- Male and female animal data were combined for the analysis. Based upon the animal data available up to 24 months it did not appear that there were any substantial differences in tumor response by sex. It was assumed that this situation would not change for any tumor response observed after 24 months.

b. Choice of Model to be Used in the Extrapolation

- Only models that provided an adequate fit to the data in the experimental range were included. This excluded such models as the one-hit model and simple linear regression.

- Models which were not available in-house or computationally convenient for use in generating risks for various environmental exposure levels were excluded from consideration. These models included the Mantel-Bryan, probit, logistic regression, Weibull (Extreme-value), and gamma-multihit models.

- It was decided that estimates of and upper confidence limits on risk should be presented from any model chosen for the extrapolation. Upper confidence limits allow for the random statistical variation in the experimental data. Lower confidence limits were not presented; instead the possiblity of an actual biologic threshold exposure level could be admitted, where any such threshold could lie above the exposure levels of regulatory concern.

- Five percent error rates were assumed to be acceptable in the generation of confidence limits on risk. Ninety-five percent upper confidence limits are commonly assumed in such extrapolations.

- The Crump or "linearized" multistage model was chosen as the model for extrapolation because it provided an adequate fit to the data and it was available and computationally convenient. Principal assumptions underlying this model and its confidence limits include:

    - additivity at low dose -- (Cancer may be initiated through a chain of genetic or epigenetic events which may already be operative and producing background tumors in the absence of the particular chemical under test.)

    - approximate low-dose linearity of the upper statistical confidence limits

  This model is also used routinely by the Carcinogen Assessment Group of EPA for estimating risks in support air and water quality criteria and standards.

Note: The choice of 95% upper confidence limits on risk from the multistage model yields conservative (or highest) estimates. Relative to the dichotomous dose-response other models now developed in risk assessment (probit, logistic regression, Weibull (Extreme-value), and gamma-multihit), the "linearized" multistage model is, for those data, the most conservative by factors ranging from 64 to 225 for upper confidence limits. However, maximum likelihood (or point estimates) of risk from this model are in very good agreement with similar estimates from the other available models. Moreover, it is obvious from a cursory examination of the table that the variation in the choice of exposure level and subpopulation has as much of an effect on the magnitude of the number of cancer cases than does the choice of maximum likelihood estimates or upper confidence limits on those estimates from the extrapolation model.

### c. Modifications to the Risk Estimates from the Model Chosen in Order to More Closely Parallel the Human Situation

- The risk estimates were adjusted from their exposure base in the animal study (six hours per day, five days per week) to correspond to the various exposure situations for each exposed human subpopulation (e.g., eight hours per day, five days per week, 50 weeks per year).

- It was assumed that human subpopulations were exposed only for proportions of their lifetimes. For most subpopulations two estimates were available: average and maximum years exposed. The average lifetime for a human was assumed to be 70 years in these calculations. The risk estimates from the model were adjusted by a proportion corresponding to the average years exposed. This resulted in generally lower and probably more realistic risk predictions than would have been obtained had lifetime exposure been assumed for these subpopulations. However, these "less-than-lifetime" risks may still overestimate human risk given that, the apparent (although preliminary) age distribution of tumors in the CIIT study appears to be nonlinear, with first tumors not appearing until around 15 months -- relatively late in the average rat lifespan.

- Perfect site concordance was assumed. This assumption does not consider that rats are obligate nose breathers while humans are not. Humans might, however, be at risk for cancer at sites other than the nasal cavity.

- No species-to-species (animal-to-human) conversions were performed on the extrapolated risk. It was assumed instead that there is equivalent formaldehyde-induced carcinogenicity for both humans and rats exposed to the same concentrations in air.

- Carcinogenic risks predicted are assumed to be risks for tumor incidence, not deaths due to tumor formation. However, if formaldehyde were a human nasal carcinogen then the one would expect these numbers would approximate risk of death, as nasal cancers in humans are often fatal. Different assumptions and analyses will be possible when data become available indicating which tumors were lethal and which, if any, were "incidental."

- Variability in response to the potential carcinogenicity of formaldehyde arising from such nonrandom sources as heterogeneity in human formation. However, if formaldehyde were a human nasal carcinogen then the one would expect these numbers would approximate risk of death, as nasal cncers in humans are often fatal. Different assumptions and analyses will be possible when data become abailable indicating which tumors were lethal and which, if any, were "incidental."

- Variability in response to the potential carcinogenicity of formaldehyde arising from such nonrandom sources as heterogeneity in human subpopulations exposed was not accounted for in the risk predictions. Such heterogeneity coud be due to age, sex, racial, and genetic differences (resistence or susceptibility) in human subpopulations. This variability is assumed to be potentially important but currently impossible to quantify.

### 4. Epidemiology

Existing epidemiologic studies are not conclusive to assess whether formaldehyde is carcinogenic or not in humans. As a consequence, no epidemiologic study can at present serve as the basis for quantitative predictions of human risk. There are several published studies of cancer risk among individuals in occupations or industries with substantial exposure to formaldehyde and other chemicals. These studies report excess cancer risk among textile workers, brickmasons, shoe makers, leather workers, and pathologists. As a group, these studies sugges that formaldehyde may be a human carcinogen, but actual levels of exposure are not documented. Some cancer case/control studies to investigate formaldehyde exposure are being initiated, but no information on these studies have been collected at this time. A major difficulty with these studies is the choice of cancer type for case selection. At least eleven on-going studies using either proportionate mortality ratio (PMR) analysis or standard ratio mortality (SMR) analysis now are focusing directly on the relationship between formaldehyde exposure and cancer (see Table A-2). Unpublished results are available for three of these studies including PMR analyses of chemical workers (Marsh 1980) and embalmers (Walrath 1980), and a SMR analysis of chemical workers (Wong 1980). However, these three studies together cover fewer than 2000 deaths. Yet, the most recent National Center for Health Statistics data reported that in the United States during 1978, there were 125 deaths (70 in males, 55 in females); that is .1 death per 100,000 people, from nose and nasal cavity cancer (Vital Statistics 1978). Thus, the probability is quite low that an analysis of 2000 deaths would reveal an increase in such a rare type of cancer. The three studies, however, do suggest some possible associatios between formaldehyde exposure and cancer, but they are inconclusive because of poor exposure documentation, possible multiple exposure, small study size, and study design limitatios. The

### Table A-2
### Summary of Studies with Findings and On-going Studies

| Type of Study | Author | Occupation or Industry | Excess Cancer | Completion Date |
|---|---|---|---|---|
| Studies with preliminary findings | | | | |
| PMR | Marsh/ Pittsburgh | Monsanto chemical workers | digestive system | - |
| PMR | Walrath/ NCI | New York embalmers | skin, brain, kidney | - |
| SMR | Wong/ Biometric Research Institute | chemical workers | prostate | - |
| On-going studies | | | | |
| PMR | Walrath/ NCI | California embalmers | | summer 1982 |
| SMR | Blair (1980)/ NCI | anatomists | | summer 1982 |
| SMR | Blair (1981)/ NCI | chemical workers | | May 1983 |
| SMR | Grauman (1979) NCI | medical technologists | | winter 1983 |
| SMR | Grauman/ NCI | histotechnologists | | summer 1982 |
| PMR/SMR | Keenlyside/ NIOSH | garment workers | | early 1982 |
| PMR/SMR | Levine/ CIIT | Canadian funeral service professionals | | summer 1982 |
| PMR/ SMR | Matonoski/ NIEHS | pathologists | hypopharynx | winter 1981 |

remaining eight on-going studies will provide more information on the carcinogenic risk of formaldehyde to humans, but they will not be completed until some time after mid-1983.

The other eight on-going studies include a second PMR study of embalmers (Walrath 1980), and seven SMR studies. These include the following occupational groups: anatomists (Blair 1981), medical technologists (Grauman 1980), histotechnologists (Grauman*) garment workers (Keenlyside**), funeral service professionals (Levine 1979), pathologists (Matanoski***), and industrial workers (Blair 1980). In general, these workers will be exposed to formaldehyde in a range from low levels to about the current Occupational Safety and Health Administration (OSHA) permissible exposure value of 3 ppm (OHSA 1978).

Statistical power calculations to assess the ability to detect meaningful relative risks were carried out on on-going studies that have information available on age distribution and person-years of follow-up beyond a possible latent period. These include Blair (1980), Blair (1981), Grauman (1979) and an unpublished study of Grauman on histological technologists. According to these calculations, together with other design considerations, and review of protocols of studies for which no power calculations are possible, the Blair (1980) study seems to have the greatest probability of detecting an increased risk of cancer. It should be noted, however, that none of the studies mentioned can detect relative risks of nasal cancer below 2 with great certainty. For this reason, because of the inherent limitation of all these studies, Dr. John Bailar in a 8/11/81 Memo to Dr. Irving Baumel expressed the view that "work in progress is not likely to resolve present concerns about formaldehyde safety".

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* Completion date summer 1982
** Completion date early 1982
*** Completion date late 1981